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(54) Title: PROSTAGLANDIN RECEPTOR LIGANDS

(57) Abstract

Compounds and methods for treating prostaglandin mediated diseases, and certain pharmaceutical compositions thereof are disclosed. The compounds are represented by formula (II): $Ar^1–W–Ar^2–X–Q$. The compounds of the invention are structurally different from NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E–type prostaglandins.

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TITLE OF THE INVENTION

PROSTAGLANDIN RECEPTOR LIGANDS

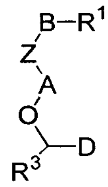
BACKGROUND OF THE INVENTION

This invention relates to compounds and methods for treating prostaglandin mediated diseases, and certain pharmaceutical compositions thereof. More particularly, the compounds of the invention are structurally different from NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E-type prostaglandins.

Two review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids: From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87. An article from *The British Journal of Pharmacology* (1994, 112, 735-740) suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord.

Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

PCT application nos WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), WO 97/00863 (January 9, 1997), WO 97/00864 (January 9, 1997), WO 96/03380 (February 8, 1996), and EP 752421-A1 (January 08, 1997) disclose compounds represented by Formula I as being useful in the treatment of prostaglandin mediated diseases.



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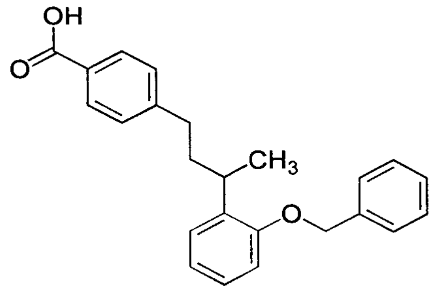


Ia

wherein:

A is phenyl, naphthyl, 5- or 6- membered heteroaryl

B is phenyl, 5- or 6- membered heteroaryl or a further defined keto-dihydro ring;

D is phenyl, 5- or 6- membered heteroaryl;

R^1 is COOH, carboxyalkyl, tetrazolyl(alkyl);

R^3 is H or alkyl, and

Z is an alkylene bridge containing 0-1 nitrogen atom or a further defined unsaturated bridge.

Compound Ia is one of the compounds specifically claimed.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula II:

$$Ar^1\text{-}W\text{-}Ar^2\text{-}X\text{-}Q$$

II

as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

Ar^1 is an aryl or heteroaryl group, optionally substituted with R^1 or R^3;

R^1 is Y_m-R^2, Y_m-Ar^3, halogen, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, $CON(R^5)_2$, $S(O)_nR^7$ or OH;

Y represents a linker between R^2 or Ar^3 and Ar^1 containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker optionally containing CO, $S(O)_n$, -C=C- or an acetylenic group, and said linker being optionally substituted by R^2;

m is 0 or 1;

n is 0, 1 or 2;

R^2 represents H, F, CHF_2, CF_3, lower alkyl or hydroxyC_{1-6} alkyl, or two R^2 groups may be joined together and represent a carbocyclic ring of up to six members, said ring containing not more than one heteroatom selected from O, N and S;

Ar^3 represents an aryl or heteroaryl group, optionally substituted with R^3 ;

R^3 is R^4, halogen, haloC_{1-6}alkyl, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, $CON(R^5)_2$, OR^4, SR^4 or $S(O)_nR^7$;

R^4 is H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3 ;

R^5 is R^4, Ph or Bn, or two R^5 groups in combination with the atom to which they are attached represent a ring of up to 6 members containing carbon atoms and up to 2 heteroatoms selected from O, N and S;

R^6 is H, F, CF_3 or lower alkyl, or two R^6 groups may be taken together and represent a ring of up to 6 members containing carbon atoms and 0-2 heteroatoms selected from O, N and S;

R^7 is lower alkyl, lower alkenyl, lower alkynyl, CHF_2, CF_3, $N(R^5)_2$, $Ph(R^8)_2$ or $CH_2Ph(R^8)_2$;

R^8 is R^4, OR^4, SR^4 or halogen

W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and optionally being substituted with R^9;

R^9 is R^2, lower alkenyl, lower alkynyl, OR^4 or SR^4;

Ar^2 represents an aryl or heteroaryl group, optionally substituted with R^3;

R^{10} represents R^4, halogen, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, OR^4, SR^4 or $S(O)_nR^7$;

X represents a linker which is attached to Ar^2 ortho to the attachment of W, said linker containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker further optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and said linker being optionally substituted with R^{11};

R^{11} is R^9;

Q represents a member selected from the group consisting of: CO_2H, tetrazole, SO_3H, hydroxamic acid, $CONHSO_2R^{12}$ and SO_2NHCOR^{12};

R^{12} represents a member selected from the group consisting of: CF_3, lower alkyl, lower alkenyl, lower alkynyl and ZAr^4 , wherein Z is an optional linker containing 0-4 carbon atoms, optionally substituted with R^{13};

R^{13} is R^9;

Ar^4 is an aryl or heteroaryl group optionally substituted with R^{14}, and

R^{14} is R^{10} or NHCOMe.

Pharmaceutical compositions and methods of treatment are also included.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds represented by formula II:

$$Ar^1\text{-}W\text{-}Ar^2\text{-}X\text{-}Q$$
$$\text{II}$$

as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

Ar^1 is an aryl or heteroaryl group, optionally substituted with R^1 or R^3;

R^1 is $Y_m\text{-}R^2$, $Y_m\text{-}Ar^3$, halogen, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, $CON(R^5)_2$, $S(O)_nR^7$ or OH;

Y represents a linker between R^2 or Ar^3 and Ar^1 containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker optionally containing CO, $S(O)_n$, -C=C- or an acetylenic group, and said linker being optionally substituted by R^2;

m is 0 or 1;

n is 0, 1 or 2;

R^2 represents H, F, CHF_2, CF_3, lower alkyl or hydroxy$C_{1\text{-}6}$ alkyl, or two R^2 groups may be joined together and represent a carbocyclic ring of up to six members, said ring containing not more than one heteroatom selected from O, N and S;

Ar^3 represents an aryl or heteroaryl group, optionally substituted with R^3 ;

R^3 is R^4, halogen, haloC_{1-6}alkyl, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, $CON(R^5)_2$, OR^4, SR^4 or $S(O)_nR^7$;

R^4 is H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3 ;

R^5 is R^4, Ph or Bn, or two R^5 groups in combination with the atom to which they are attached represent a ring of up to 6 members containing carbon atoms and up to 2 heteroatoms selected from O, N and S;

R^6 is H, F, CF_3 or lower alkyl, or two R^6 groups may be taken together and represent a ring of up to 6 members containing carbon atoms and 0-2 heteroatoms selected from O, N and S;

R^7 is lower alkyl, lower alkenyl, lower alkynyl, CHF_2, CF_3, $N(R^5)_2$, $Ph(R^8)_2$ or $CH_2Ph(R^8)_2$;

R^8 is R^4, OR^4, SR^4 or halogen

W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and optionally being substituted with R^9;

R^9 is R^2, lower alkenyl, lower alkynyl, OR^4 or SR^4;

Ar^2 represents an aryl or heteroaryl group, optionally substituted with R^3;

R^{10} represents R^4, halogen, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, OR^4, SR^4 or $S(O)_nR^7$;

X represents a linker which is attached to Ar^2 ortho to the attachment of W, said linker containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker further optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and said linker being optionally substituted with R^{11};

R^{11} is R^9;

Q represents a member selected from the group consisting of: CO_2H, tetrazole, SO_3H, hydroxamic acid, $CONHSO_2R^{12}$ and SO_2NHCOR^{12};

R^{12} represents a member selected from the group consisting of: CF_3, lower alkyl, lower alkenyl, lower alkynyl and ZAr^4 , wherein Z is an optional linker containing 0-4 carbon atoms, optionally substituted with R^{13};

R^{13} is R^9;

Ar^4 is an aryl or heteroaryl group optionally substituted with R^{14}, and

R^{14} is R^{10} or NHCOMe.

As used herein, the following terms and definitions apply unless indicated otherwise.

The following abbreviations have the indicated meanings:

Ac	=	acetyl
AIBN	=	2,2'-azobisisobutyronitrile
Bn	=	benzyl
DHP	=	2,3-dihydro-4H-pyran
DIBAL	=	diisobutyl aluminum hydride
DIPHOS	=	1,2-bis(diphenylphosphino)ethane
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
EDCI	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	=	triethylamine
Fur	=	furandiyl
HBBS	=	Hanks balanced salt solution
HEPES	=	N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]
KHMDS	=	potassium hexamethyldisilazane
LDA	=	lithium diisopropylamide
LPS	=	lipopolysaccharide
MCPBA	=	metachloroperbenzoic acid
MES	=	2-[N-morpholino]ethanesulfonic acid
Ms	=	methanesulfonyl = mesyl
MsO	=	methanesulfonate = mesylate
NBS	=	N-bromosuccinimide
NCS	=	N-chlorosuccinimide
NSAID	=	non-steroidal anti-inflammatory drug
PCC	=	pyridinium chlorochromate

PDC	=	pyridinium dichromate
Ph	=	phenyl
Phe	=	benzenediyl
PPTS	=	pyridinium p-toluenesulfonate
pTSA	=	p-toluenesulfonic acid
Pye	=	pyridinediyl
r.t.	=	room temperature
rac.	=	racemic
Tf	=	trifluoromethanesulfonyl = triflyl
TfO	=	trifluoromethanesulfonate = triflate
Th	=	2- or 3-thienyl
THF	=	tetrahydrofuran
Thi	=	thiophenediyl
THP	=	tetrahydropyran-2-yl
Thz	=	thiazol-2-yl
TLC	=	thin layer chromatography
Ts	=	p-toluenesulfonyl = tosyl
TsO	=	p-toluenesulfonate = tosylate
Tz	=	1H (or 2H)-tetrazol-5-yl
C_3H_5	=	allyl

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

The terms alkyl, alkenyl, and alkynyl mean linear, branched, and cyclic structures and combinations thereof.

"Alkyl" and the alkyl portions of alkoxy, arylalkyl, alkylaryl and the like include "cycloalkyl" and "lower alkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl-4-propylnonyl, and the like.

"Lower alkyl" includes "lower cycloalkyl" and means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, and the like.

"Cycloalkyl" includes "lower cycloalkyl" and means a hydrocarbon, containing one or more rings of from 3 to 12 carbon atoms, with the hydrocarbon having up to a total of 20 carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1- bicyclo[4.4.0]decyl, and the like.

"Lower cycloalkyl" means a hydrocarbon containing one or more rings of from 3 to 7 carbon atoms, with the hydrocarbon having up to a total of 7 carbon atoms. Examples of lower cycloalkyl groups are cyclopropyl, cyclopropylmethyl, cyclobutyl, 2-cyclopentylethyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, and the like.

The term "alkenyl" includes "cycloalkenyl" and "lower alkenyl" and means alkenyl groups of 2 to 20 carbon atoms. Examples of alkenyl groups include allyl, 5-decen-1-yl, 2-dodecen-1-yl, and the like.
"Lower alkenyl" includes "lower cycloalkenyl" and means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Cycloalkenyl" includes "lower cycloalkenyl" and means alkenyl groups of 3 to 20 carbon atoms, which include a ring of 3 to 12 carbon atoms, and in which the alkenyl double bond may be located anywhere in the structure. Examples of cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-vinyladamant-1-yl, 5-methylene-dodec-1-yl and the like.

"Lower cycloalkenyl" means alkenyl groups of 3 to 7 carbon atoms, which include a ring of 3 to 7 carbon atoms and in which the double bond may be located anywhere in the structure. Examples of lower cycloalkenyl groups are cyclopropen-1-yl, cyclohexen-3-yl, 2-cyclopentylethen-1-yl, and the like.

The term "alkynyl" includes "cycloalkynyl" and "lower alkynyl" and means alkynyl groups of 2 to 20 carbon atoms. Examples of alkynyl groups are ethynyl, 2-pentadecyn-1-yl, 1-eicosyn-1-yl, and the like.

"Lower alkynyl" includes "lower cycloalkynyl" and means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkynyl" includes "lower cycloalkynyl" and means alkynyl groups of 5 to 20 carbon atoms, which include a ring of 3 to 20 carbon atoms. The alkynyl triple bond may be located anywhere in the group, with the proviso that if it is within a ring, such a ring must be of 10 members or greater. Examples of cycloalkynyl are cyclododecyn-3-yl, 3-cyclohexyl-1-propyn-1-yl, and the like.

"Lower cycloalkynyl" means alkynyl groups of 5 to 7 carbon atoms which include a ring of 3 to 5 carbon atoms. Examples of lower cycloalkynyl are cyclopropylethynyl, 3-(cyclobutyl)-1-propynyl, and the like.

Halogen includes F, Cl, Br and I. When a group is "halogenated", it is substituted with one or more halogen atoms, up to the maximum number of positions available for substitution, i.e., it is "perhalogenated".

The definition of any substituent (e.g., R^6, R^{10}, etc.) in a particular molecule is independent of its definition elsewhere in the molecule. Thus, $-N(R^5)_2$ represents $-NHH$, $-NHCH_3$, $-NHC_6H_5$, and the like.

Examples of rings formed when two R^2 groups join include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, oxetane, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, pyrrolidine and piperidine.

The heterocycles formed when two R^5 groups join through N include pyrrolidine, piperidine, morpholine, thiamorpholine, piperazine and N-methylpiperazine.

Aryl and the aryl portions of arylalkyl, aryloxy, arylalkoxy and the like refer to aromatic as well as partially aromatic 6-12 membered ring systems. Examples include benzene, naphthalene, biphenyl and tetrahydronaphthalene.

Heteroaryl and the heteroaryl portion of heteroarylalkyl, heteroarylalkoxy, heteroaryloxy and the like refer to 5-15 membered aromatic

and partially aromatic ring systems, containing 1-4 heteroatoms selected from O, S and N. Examples include pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, benzothiazole, 1,3,4-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, pyrrole and methylenedioxyphenyl.

Haloaryl and haloheteroaryl refer to aryl and heteroaryl groups respectively having at least one halo atom attached, up to perhalogenated, as indicated above. Haloalkyl refers to alkyl groups which have one or more halogen atoms attached, including up to the maximum number of positions which can be substituted, i.e., perhalogenated alkyl groups. In haloalkylarylalkoxy, the terminal alkyl portion is halogenated. In haloarylalkoxy, the aryl portion is halogenated, and in haloheteroarylalkoxy the heteroaryl portion is halogenated.

Aryl, heteroaryl and other groups are termed optionally substituted as described herein. When a moiety is optionally substituted, this means that the moiety is unsubstituted or is substituted with 1-5 of the substituent groups, as permitted with respect to the availability for substitution. In particular, this applies to Ar^1, which is optionally substituted with 1-5 R^1 and/or R^3 groups. Y is optionally substituted with 1-5 R^2 groups. Ar^3 is optionally substituted with 1-5 R^3 groups. W is optionally substituted with 1-5 R^9 groups. Ar^2 is optionally substituted with 1-5 R^3 groups. X is optionally substituted with 1-5 R^{11} groups. Z is optionally substituted with 1-5 R^{13} groups, and Ar^4 is optionally substituted with 1-5 R^{14} groups.

Y represents an optional linking group between Ar^1 and R^2 or R^3. When m is 0, Y is absent and when m is 1, Y is present. The linking group contains 0-4 carbon atoms and 0-1 heteroatoms selected from O, S and N, and further is optionally substituted with R^2. Examples of suitable linking groups include: O, S, NR^2, OCH_2, CH=CH, SO_2CH_2, $NHCHMeCH_2$,O, CH_2, CH_2CH=CH and the like.

W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and optionally being substituted with R^9. Examples include OCH_2CH_2, CH=$CHCH_2$, $CH_2SO_2CH_2$, $NHCHMeCH_2$, $(CH_2)_5$, CH_2CH=$CHCH_2$, $O(CH_2)_3O$, CH_2NHCO, $CH_2C{+}C$, CH_2OCH_2, CH_2CH=CH, 1,2-c-Pr-CH_2, CH_2-1,2-c-Pr and the like.

X represents a linker that is attached to Ar^2 ortho to the attachment of W. The linker contains 0-4 carbon atoms and not more than one heteroatom selected from O, N and S. Linker X further optionally contains a group CO, $S(O)_n$, C=C or an acetylenic group, and said linker is optionally substituted with R^{11}. Examples of X include OCH_2, CH=CH, SO_2CH_2, $NHCHMeCH_2$,O, CH_2, CH_2 CH=CH, 1,2-c-Pr, $(CH_2)_2O$, C+C and the like.

In ZAr^4 , Z represents an optional linker having 0-4 carbon atoms, and being optionally substituted with R^{13}. Examples of such a linker include a bond, CH_2CH_2, CH=CH, $CHMeCH_2$, CH_2, CH_2CH=CH, 1,2-c-Pr, and the like.

One aspect of the invention that is of particular interest relates to compounds of formula II wherein R^1 is OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 or $NR^2CH_2Ar^3$. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Ar^3 is an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R^3. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Ar^2 is an aryl or heteroaryl group selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with 1-5 groups selected from R^4, OR^4, SR^4 and halogen.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, CH_2CH=CH, CH=$CHCH_2$, CH(OH)CH=CH, CH=CHCH(OH), CH_2C+C, C+CCH_2 , 1,2-c-Pr-CH_2 and -1,2-c-Pr-CH_2-. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein X is selected from the group consisting of: $(CH_2)_2$, CH=CH, C+C and 1,2-c-Pr. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Q is CO_2H or tetrazole. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Z represents a 0-2 carbon atom linker that is unsubstituted. Within this subset, all other variables are as originally defined.

Another aspect of the invention that is of particular interest relates to compounds of formula II wherein Ar^4 represents an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, said group being optionally substituted with R^3. Within this subset, all other variables are as originally defined.

A preferred aspect of the invention relates to compounds represented by formula II wherein:

Ar^1 is an aryl or heteroaryl group substituted by R^1 and R^3;

R^1 is OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 or $NR^2CH_2Ar^3$;

Ar^3 is selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R^3;

Ar^2 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, and thiazole, said group being optionally substituted with 1-4 members selected from the group consisting of: R^4, OR^4, SR^4 and halogen;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, $CH(OH)CH{=}CH$, $CH{=}CHCH(OH)$, $CH_2C{+}C$, $C{+}CCH_2$ 1,2-c-Pr-CH_2- and -CH_2-1,2-c-Pr-;

X is selected from the group consisting of: $(CH_2)_2$, $CH{=}CH$, $C{+}C$ and 1,2-c-Pr;

and Q is CO_2H or tetrazole. Within this subset, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds represented by formula II wherein:

Ar^1 is an aryl or heteroaryl group optionally substituted with R^1 and R^3;

R^1 is OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 or $NR_2CH_2Ar^3$;

Ar^3 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being optionally substituted with R^3;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, CH(OH)CH=CH, CH=CHCH(OH), $CH_2C{+}C$ or $C{+}CCH_2$;

Ar^2 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being optionally substituted with R^8;

X is is selected from the group consisting of: $(CH_2)_2$, CH=CH, C+C and 1,2-c-Pr;

Q is $CONHSO_2ZAr^4$;

Z is a 0-2 carbon linker and is unsubstituted;

Ar^4 is selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, and is optionally substituted by R^3. Within this subset, all other variables are as originally defined.

A more preferred aspect of the invention relates to compounds represented by formula II wherein:

Ar^1 is benzene or thiophene substituted in position 2 and/or position 4 relative to the attachment of W with a member selected from the group consisting of: OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 and $NR^2CH_2Ar^3$, and is optionally substituted in position 3 with a member selected from the group consisting of: OMe, $OCHF_2$ and lower alkyl;

Ar^3 is benzene or thiophene, optionally substituted with R^8;

W is selected from the group consisting of: CH_2OCH_2, $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, CH(OH)CH=CH and CH=CHCH(OH),

Ar^2 is benzene or thiophene, optionally substituted with 1-4 members selected from R^4, OR^4, SR^4 and halogen;

X represents a member selected from the group consisting of: $(CH_2)_2$, CH=CH and 1,2-c-Pr, and

Q is CO_2H.

Within this subset, all other variables are as originally defined.

Another more preferred aspect of the invention relates to compounds represented by formula II wherein:

Ar^1 is a benzene or a thiophene unsubstituted or substituted in position 2 and/or position 4 relative to the point of attachment to W by a member selected from the group consisting of: OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 and $NR^2CH_2Ar^3$; and is optionally substituted at position 3 with one member selected from the group consisting of: OMe, $OCHF_2$ and lower alkyl;

Ar^3 is benzene or thiophene, optionally substituted with R^8;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, $CH(OH)CH{=}CH$ and $CH{=}CHCH(OH)$;

Ar^2 is benzene or thiophene, optionally substituted with $R4$, $OR4$, $SR4$ or halo;

X is selected from the group consisting of: $(CH_2)_2$, $CH{=}CH$ and 1,2-c-Pr,

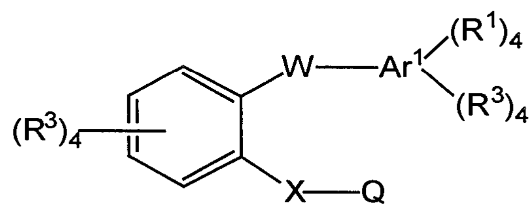
Q is $CONHSO_2ZAr^4$,

Z is a bond or CH_2, and

Ar^4 is selected from the group consisting of: benzene, thiophene, 1,3,4-thiadiazole and naphthalene and is substituted with R^8.

Within this subset, all other variables are as originally defined.

A particularly preferred aspect of the present invention that is of interest relates to compounds represented by formula II':



II'

as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

Ar^1 represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;

R^1 represents H, OH, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;

R^3 represents R^4, halogen, OR^4 or SR^4;

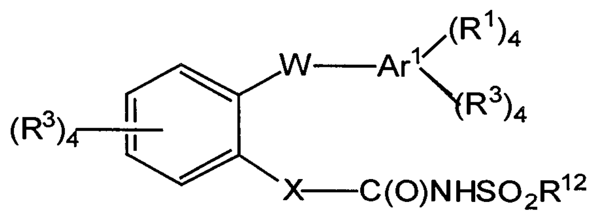
R^4 represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3;

X represents a member selected from the group consisting of: $-(CH_2)_{1-2}-$, 1,2-c-Pr, -CH=CH-, $-CH_2O-$, $-C{+}CCH_2-$, -C+C-, and $-CH_2-C{+}C-$;

W represents a member selected from the group consisting of: $-(CH_2)_{3-6}-$, $-CH_2CH{=}CH-$, $-CH{=}CHCH_2-$, -CH(OH)CH=CH-, -CH=CHCH(OH)-, $-CH_2$-1,2-c-Pr-, -1,2-c-Pr-CH_2-, , $-CH_2-O-CH_2-$, $-O-(CH_2)_{1-3}$ -O- , $-CH_2$-NHC(O)-, $-CF_2CH{=}CH-$, $-CH{=}CHCF_2-$, $-CH_2CH_2-S-$, $-S-CH_2CH_2-$, $-CH_2CH_2-SO_2-$, $-SO_2-CH_2CH_2-$, $-O-(CH_2)_{1-3}-$, $-(CH_2)_{1-3}-O-$ and $-CH{=}CHCH_2CH_2-$, and

all other variables are as originally defined.

Another particularly preferred aspect of the invention relates to compounds represented by formula II":



II"

as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

Ar^1 represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;

R^1 represents H, OH, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;

R^3 represents R^4, halogen, OR^4 or SR^4;

R^4 represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3;

X represents a member selected from the group consisting of: -$(CH_2)_{1-2}$-, -1,2-c-Pr-, -CH=CH-, -CH_2O-, -C+CCH_2-, -C+C-, and -CH_2-C+C-;

W represents a member selected from the group consisting of: -$(CH_2)_{3-6}$-, -CH_2CH=CH-, -CH=$CHCH_2$-, -CH(OH)CH=CH-, -CH=CHCH(OH)-, -CH_2-1,2-c-Pr-, -1,2-c-Pr-CH_2-, -CH_2-O-CH_2-, -O-$(CH_2)_{1-3}$-O- , -CH_2-NHC(O)-, -CF_2CH=CH-, -CH=$CHCF_2$-, -CH_2CH_2-S-, -S-CH_2CH_2-, -CH_2CH_2-SO_2-, -SO_2-CH_2CH_2-, -O-$(CH_2)_{1-3}$-, -$(CH_2)_{1-3}$-O- and -CH=$CHCH_2CH_2$- , and

R^{12} is selected from the group consisting of: C_{1-6}alkyl, thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl, -CH=CH-phenyl, said thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl and -CH=CH-phenyl groups being optionally substituted with R^3.

Examples of compounds within the present application are the following:

Table I

(Ar^1-W-Ar^2-X-Q)

Ex	Ar^1	W	Ar^2	X	Q
1	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	$(CH_2)_2$	CO_2H
2	2-(BnO)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	$CONHSO_2$ -2-thienyl
3	2-(BnO)-3-MePh	CH=$CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-2-thienyl
4	2-((2-Cl-4-FPh) CH_2O)-3-CF_3Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
5	2-((2-Cl-4-FPh) CH_2O)-3-CF_3Ph	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2H
6	2-(BnO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2Na
7	2-(BnO)Ph	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2Na

8	4-(BnO)-3,5-$(MeO)_2$Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2Na
9	4-(BnO)-3,5-$(MeO)_2$Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
10	2-(BnO)-5-AcPh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
11	2-(BnO)-5-AcPh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
12	2-(BnO)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2Na
13	2-(BnO)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
14	4-(BnO)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2Na
15	4-(BnO)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
16	2-(BnO O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH_2	CO_2Na
17	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH_2	CO_2Na
18	2-(BnO)-3-MePh	$CH_2CH=CH$	5-Cl-1,2-Phe	CH_2	CO_2Na
19	2-(BnO)-3-MePh	$CH=CHCH_2$	5-Cl-1,2-Phe	CH_2	CO_2Na
20	4-(BnO)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	1,2-c-Pr	CO_2H
21	2-(BnO)-3-MePh	$CH=CHCH_2$	4,5-$(MeO)_2$-1,2-Phe	CH=CH	CO_2H
22	2-(BnO)-3-MePh	$CH_2CH=CH$	4,5-$(MeO)_2$-1,2-Phe	CH=CH	CO_2H
23	3,4-(methylene dioxy)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
24	3,4-(methylene dioxy)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
25	Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
26	Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
27	2-(HO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
28	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
29	2-(BnO)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2Na
30	2-((7-Cl-2-quinolinyl)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
31	2-((7-Cl-2-quinolinyl)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
32	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	bond	CO_2H
33	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	bond	CO_2Na
34	2-(BnO)-3-MePh	$CH_2CH=CH$	1,2-Phe	bond	CO_2Na
35	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	CH=CH	CO_2Na
36	2-(BnO)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	CO_2Na
37	4-(BnO)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	CO_2Na

38	4-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
39	4-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
40	3,4-$(MeO)_2$Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
41	3,4-$(MeO)_2$Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
42	2-(BnO)Ph	CH(OH)CH=CH	1,2-Phe	CH=CH	CO_2Na
43	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	$(CH_2)_2$	$CONNaSO_2$-2-thienyl
44	4-(BnO)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CONNaSO_2$-2-thienyl
45	4-(BnO)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONNaSO_2$-2-thienyl
46	2-(BnO)-3-MePh	CH_2-1,2-c-Pr	1,2-Phe	CH=CH	CO_2Na
47	2-(BnO)-3-MePh	1,2-c-Pr-CH_2	1,2-Phe	CH=CH	CO_2Na
48	2-(BnO)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO_2Na
49	2-(BnO)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
50	2-((2,6-Cl_2Ph)CH_2O)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
51	2-((2,6-Cl_2Ph)CH_2O)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO_2H
52	2-((4-FPh)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
53	2-((4-FPh)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
54	2-((3,4-F_2Ph)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
55	2-((3,4-F_2Ph)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
56	2-((3,5-F_2Ph)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
57	2-((3,5-F_2Ph)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
58	2-((2,6-Cl_2Ph)CH_2O)-3-($HOCH_2$)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
59	2-((2,6-Cl_2Ph)CH_2O)-3-($HOCH_2$)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
60	2-((2,6-Cl_2Ph)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
61	2-((2,6-Cl_2Ph)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2Na
62	2-((4-CF_3Ph)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H

63	2-((4-CF_3Ph) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2Na
64	2-((4-(CHF_2O)Ph) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
65	2-((4-(CHF_2O) Ph)CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2Na
66	2-((4-CF_3Ph) CH_2O)-3-(HOCH_2)Ph	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
67	2-((4-CF_3Ph) CH_2O)-3-(HOCH_2)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
68	2-((4-CF_3Ph) CH_2O)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
69	2-(PhCH_2O)-3-(HOCH_2)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
70	3-(PhO)Ph	CH_2OCH_2	1,2-Phe	CH=CH	CO_2Na
71	2-(PhO)Ph	CH_2OCH_2	1,2-Phe	CH=CH	CO_2Na
72	3-(BnO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2Na
73	3-(BnO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2Na
74	2-(BnO)Ph	O(CH_2)$_3$O	1,2-Phe	CH=CH	CO_2Na
75	2-(PhCHMeO)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2Na
76	2-(PhCHMeO)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
77	3-(PhO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2Na
78	3-(PhO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2Na
79	3-Ph benzofuran-7-yl	CH=CHCH_2	1,2-Phe	CH=CH	CO_2Na
80	3-Ph benzofuran-7-yl	CH_2CH=CH	1,2-Phe	CH=CH	CO_2Na
81	Ph	CH=CHCH_2	1,2-Phe	CH=CH	CONHSO_2-2-thienyl
82	Ph	CH_2CH=CH	1,2-Phe	CH=CH	CONHSO_2-2-thienyl
83	4-(MeO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CONHSO_2-2-thienyl
84	4-(MeO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CONHSO_2-2-thienyl
85	2-(BnO)-1-naphthyl	CH_2NHCO	1,2-Phe	CH=CH	CO_2H
86	2-((2-Cl-4-FPh) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
87	2-((2-Cl-4-FPh) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H

88	2-((2,4-F_2Ph) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
89	2-((2,4-F_2Ph) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
90	2-((2,4,6-F_3Ph) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
91	2-((2,4,6-F_3Ph) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
92	2-((2,6-Cl_2-4-FPh) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
93	2-((2,6-Cl_2-4-FPh) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
94	2-((2,4-F_2Ph)CH_2O) -3-(CHF_2O)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
95	2-((2,4-F_2Ph) CH_2O) -3-(CHF_2O)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
96	2-((4-FPh)CH_2O) -3-MePh	CF_2CH=CH	1,2-Phe	CH=CH	CO_2H
97	2-((4-FPh)CH_2O) -3-MePh	CH=CHCF_2	1,2-Phe	CH=CH	CO_2H
98	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_3$	1,2-Phe	CH=CH	CONHSO_2-(4-i-PrPh)
99	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_3$	1,2-Phe	CH=CH	CONHSO_2-(4-t-BuPh)
100	2-((4-FPh)CH_2O) -3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CONHSO_2-(4-(MeO)Ph)
101	2-((4-FPh)CH_2O) -3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CONHSO_2-(2,3-Cl_2Ph)
102	2-((4-FPh)CH_2O) -3-MePh	CH=CHCH_2	4-Cl-1,2-Phe	CH=CH	CONHSO_2-(5-Br-2-(MeO)Ph)
103	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_2$S	3-F-1,2-Phe	CH=CH	CONHSO_2-(2,3,4-Cl_3Ph)
104	2-((4-FPh) CH_2O)-3-MePh	$(CH_2)_2$S	6-CF_3-1,2-Phe	CH=CH	CONHSO_2-(5-F-2-MePh)
105	2-((4-FPh) CH_2O)-3-MePh	$(CH_2)_2$S	4,5-F_2-1,2-Ph	CH=CH	CONHSO_2-(2,5-Me_2Ph)
106	2-((4-FPh) CH_2O)-3-MePh	$(CH_2)_2SO_2$	1,2-Phe	CH=CH	CONHSO_2-(4-CF_3Ph)
107	2-((4-FPh) CH_2O)-3-MePh	$(CH_2)_2SO_2$	1,2-Phe	CH=CH	CONHSO_2-2-naphthyl
108	2-((4-FPh) CH_2O)-3-MePh	CH=CHCH_2	3-F-1,2-Phe	CH=CH	CONHSO_2-(3-Cl-4-FPh)

109	2-((4-FPh) CH_2O)-3-MePh	$SO_2(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(4-n-PrPh)
110	2-((4-FPh) CH_2O)-3-(MeO)Ph	$SO_2(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2-ClPh)
111	2-((4-FPh) CH_2O)-3-(MeO)Ph	$SO_2(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(4-FPh)
112	2-((4-FPh) CH_2O)-3-(MeO)Ph	$S(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2-PhPh)
113	2-((4-FPh) CH_2O)-3-(MeO)Ph	$S(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2-CF_3Ph)
114	2-((4-FPh) CH_2O)-3-(MeO)Ph	$S(CH_2)_2$	4-t-Bu-1,2-Phe	CH=CH	$CONHSO_2$-(4-Cl-2,5-Me_2Ph)
115	2-((4-FPh) CH_2O)-3-(MeO)Ph	$O(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2,5-Cl_2Ph)
116	2-((4-FPh) CH_2O)-3-(MeO)Ph	$O(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-(4-Br-2-(CF_3O)Ph)
117	2-((4-FPh) CH_2O)-3-(MeO)Ph	$O(CH_2)_2$	1,2-Phe	CH=CH	$CONHSO_2$-CH_2Ph
118	2-((4-FPh) CH_2O)-3-(MeO)Ph	$(CH_2)_2O$	1,2-Phe	CH=CH	$CONHSO_2$-1-naphthyl
119	2-((4-FPh) CH_2O)-3-(MeO)Ph	$(CH_2)_2O$	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(2-FPh)
120	2-((4-FPh) CH_2O)-3-(MeO)Ph	$(CH_2)_2O$	1,2-Phe	CH=CH	$CONHSO_2$-(2,4-Cl_2Ph)
121	2-((4-FPh) CH_2O)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	$CONHSO_2$-CH=CHPh
122	2-((4-FPh)CH_2O)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	$CONHSO_2$-(3,5-$(CF_3)_2$Ph)
123	2-((4-FPh)CH_2O)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	$CONHSO_2$-(2,5-Cl_2-3-thienyl)
124	2-((4-FPh) CH_2O)Ph	$(CH_2)_4$	3-F-1,2-Phe	CH=CH	$CONHSO_2$-(3-BrPh)
125	2-((4-FPh) CH_2O)Ph	$(CH_2)_4$	3-MeO-1,2-Phe	CH=CH	$CONHSO_2$-(2-BrPh)

126	2-((4-FPh) CH_2O)Ph	$(CH_2)_4$	1,2-Phe	CH=CH	$CONHSO_2$-(2-NO_2Ph)
127	2-((4-FPh) CH_2O)Ph	$(CH_2)_5$	1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(3-ClPh)
128	2-((4-FPh) CH_2O)Ph	$(CH_2)_5$	1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(4-(CF_3O)Ph)
129	2-HOPh	CH=CH$(CH_2)_2$	1,2-Phe	$(CH_2)_2$	$CONHSO_2$-8-quinolinyl
130	2-((4-FPh) CH_2O)Ph	CH=CH$(CH_2)_2$	5-(CF_3O)-1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(3,4-Cl_2Ph)
131	4-((2,6-Cl_2-4-FPh)CH_2O)-3-MePh	CH=CH$(CH_2)_2$	3-F-1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(4-EtPh)
132	2-((4-FPh) CH_2O)Ph	CH_2CH=CH	1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(4-Cl-2-NO_2Ph)
133	2-((4-FPh) CH_2O)Ph	CH=CHCH_2	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(2-Cl-3-Br-5-thienyl)
134	2-((4-FPh) CH_2O)Ph	CH_2CH=CH	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(3,4-$(MeO)_2$Ph)
135	2-HOPh	CH=CHCH_2	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(2,5-Cl_2-3-Br-4-thienyl)
136	4-((4-FPh)CH_2O)-3-(MeO)Ph	CH_2CH=CH	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(4-Br-2,5-F_2Ph)
137	4-((4-FPh)CH_2O)-3-(MeO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	$CONHSO_2$-(5-(AcNH)-1,3,4-thiadiazol-2-yl)
138	4-((4-FPh) CH_2O)-3-(MeO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	$CONHSO_2$-(2,3,4,5,6-F_5Ph)
139	4-((2-Cl-4-FPh) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	$CONHSO_2$-(2-CNPh)
140	2-((4-FPh) CH_2O)Ph	CH_2CH=CH	4-F-1,2-Phe	CH=CH	$CONHSO_2$-(2-Cl-6-MePh)
141	2-HOPh	CH=CHCH_2	1,2-Phe	CH=CH	$CONHSO_2$-(2,4,6-Me_3Ph)
142	Ph	CH_2CH=CH	1,2-Phe	CH=CH	$CONHSO_2$-(2,3-Br_2-2-thienyl)
143	2-((4-FPh) CH_2O)Ph	CH=CHCH_2	1,2-Phe	CH_2O	$CONHSO_2$-(4-NO_2Ph)
144	2-((4-FPh) CH_2O)Ph	CH_2CH=CH	1,2-Phe	CH_2O	$CONHSO_2$-(3,5-Cl_2Ph)
145	2,4-((4-FPh) $CH_2O)_2$Ph	CH=CHCH_2	1,2-Phe	prop-1-yne-1,3-diyl	$CONHSO_2$-(5-Cl-2-thienyl)

146	4-((2,4-F_2Ph) CH_2O)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH_2O	$CONHSO_2$-(4-CF_3Ph)
147	2-HO-3-MePh	$CH=CHCH_2$	1,2-Phe	CH_2O	$CONHSO_2$-(2,4-F_2Ph)
148	2-((4-FPh) CH_2O)Ph	$CH_2CH=CH$	4-F-1,2-Phe	1,2-ethyne diyl	$CONHSO_2$-(4-ClPh)
149	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	1,2-ethyne diyl	$CONHSO_2$-(3-CF_3Ph)
150	4-HOPh	$CH_2CH=CH$	1,2-Phe	1,2-ethyne diyl	$CONHSO_2$-Ph
151	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	prop-2-yne-1,3-diyl	$CONHSO_2$-(5-Br-2-thienyl)
152	2,4-((4-FPh) $CH_2O)_2$Ph	$CH_2CH=CH$	1,2-Phe	1,2-ethynediyl	$CONHSO_2$-Me
153	2,4-((4-FPh) $CH_2O)_2$Ph	$CH=CHCH_2$	1,2-Phe	1,2-c-Pr	$CONHSO_2$-(2,5-$(MeO)_2$Ph)
154	6-((4-FPh) CH_2O)-2-naphthyl	$CH_2CH=CH$	4-F-1,2-Phe	1,2-c-Pr	$CONHSO_2$-(3-MePh)
155	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	1,2-c-Pr	$CONHSO_2$-(4-MePh)
156	4-HO-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	1,2-c-Pr	$CONHSO_2$-n-Bu
157	4-((4-FPh)CH_2O)-1-naphthyl	$CH=CHCH_2$	1,2-Phe	1,2-c-Bu	$CONHSO_2$-(2-Cl-4-FPh)
158	Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CONHSO_2$-(2-MePh)
159	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-c-Pr
160	2,4-((4-FPh) $CH_2O)_2$Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
161	4-((2,4-F_2Ph) CH_2O)-3-(MeO)Ph	$(CH_2)_3$	4-F-1,2-Phe	CH=CH	1H-tetrazol-5-yl
162	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	3-MeO-1,2-Phe	CH=CH	1H-tetrazol-5-yl
163	2,4-((4-FPh) $CH_2O)_2$Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	1H-tetrazol-5-yl
164	4-HO-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	1,2-c-Pr	1H-tetrazol-5-yl
165	Ph	$CH=CHCH_2$	1,2-Phe	$(CH_2)_2$	1H-tetrazol-5-yl
166	2-((4-FPh)CH_2O)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	SO_3H
167	2-((4-FPh)CH_2O)-3-MePh	$(CH_2)_3$	4-F-1,2-Phe	$(CH_2)_2$	SO_3H

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc salts, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred

are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula II are meant to also include the pharmaceutically acceptable salts and hydrates.

Dose Ranges

The magnitude of a prophylactic or therapeutic dose of a compound of Formula II will, of course, vary with the nature and the severity of the condition to be treated and with the particular compound of Formula II and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from as low as about 0.5 mg to as high as about 5 g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage units will generally contain between from about 1 mg to about 2 g of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a compound of Formula II as an active ingredient or a pharmaceutically acceptable salt or hydrate, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

For the treatment of any of the prostanoid mediated diseases compound II may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin

capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional

excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound II may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula II are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The composition of the present invention may also include additional therapeutic agents. For example, conventional analgesics such as aspirin or acetaminophen may be incorporated into the composition. Other examples of additional therapeutic agents which can be included are NSAIDs, such as ibuprofen or naproxen, COX-2 selective compounds, such as those which are described in the following patents and published applications: WO96/25405, U.S.Pat. No. 5,633,272, WO97/38986, U. S. Pat. No. 5,466,823, WO98/03484, WO97/14691 and WO95/00501, and other compounds.

Utilities

The ability of the compounds of Formula II to interact with prostaglandin receptors makes them useful for preventing or reversing undesirable symptoms caused by prostaglandins in a mammalian, especially human, subject. This mimicking or antagonism of the actions of prostaglandins indicates that the compounds and pharmaceutical compositions thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: Pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures as well as immune and autoimmune diseases. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compounds of formula II is also of use in the

treatment and/or prevention prostaglandin-mediated proliferation disorders such as may occur in diabetic retinopathy and tumor angiogenesis.

Compounds of formula II inhibit prostanoid-induced smooth muscle contraction by antagonizing contractile prostanoids or mimicking relaxing prostanoids and hence may be use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, the treatment of glaucoma, for the prevention of bone loss (treatment of osteoporosis) and for the promotion of bone formation (treatment of fractures) and other bone diseases such as Paget's disease.

By virtue of its prostanoid or prostanoid antagonist activity, compound II are useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contraindicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; thrombosis, occlusive vascular diseases; those prior to surgery or taking anti-coagulants. Compound II will also be useful as a cytoprotective agent for patients undergoing chemotherapy.

Consequently one aspect of the invention addresses a method of treating or preventing a prostaglandin mediated disease in a mammalian patient in need thereof, comprising admininstering to said patient a compound in accordance withformula II in an amount which is effective for treating or preventing said prostaglandin mediated disease.

In another aspect of the invention, a method of treating or preventing a prostaglandin mediated disease is described which is further comprised of administering to said patient an effective amount of a COX-2 selective inhibiting compound.

More particularly, a method of treating or preventing a prostaglandin mediated disease is addressed wherein the prostaglandin mediated disease is selected from the group consisting of:

pain, fever, inflammation, rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and

neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains, strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout, ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures, immune and autoimmune diseases, cellular neoplastic transformations, metastatic tumor growth, prostaglandin-mediated proliferation disorders such as diabetic retinopathy and tumor angiogenesis, dysmenorrhea, premature labor, asthma, eosinophil related disorders, Alzheimer's disease, glaucoma, bone loss (osteoporosis), promotion of bone formation (treatment of fractures) and other bone diseases such as Paget's disease.

Further, a method of treating or preventing an E type prostaglandin mediated disease in a mammalian patient is described herein, comprising administering to said patient an amount of an E type prostaglandin ligand in an amount which is effective to treat or prevent said E type prostaglandin mediated disease.

More particularly, the method described with respect to E-typ prostaglandin mediated diseases further comprises administering a COX-2 selective inhibitor.

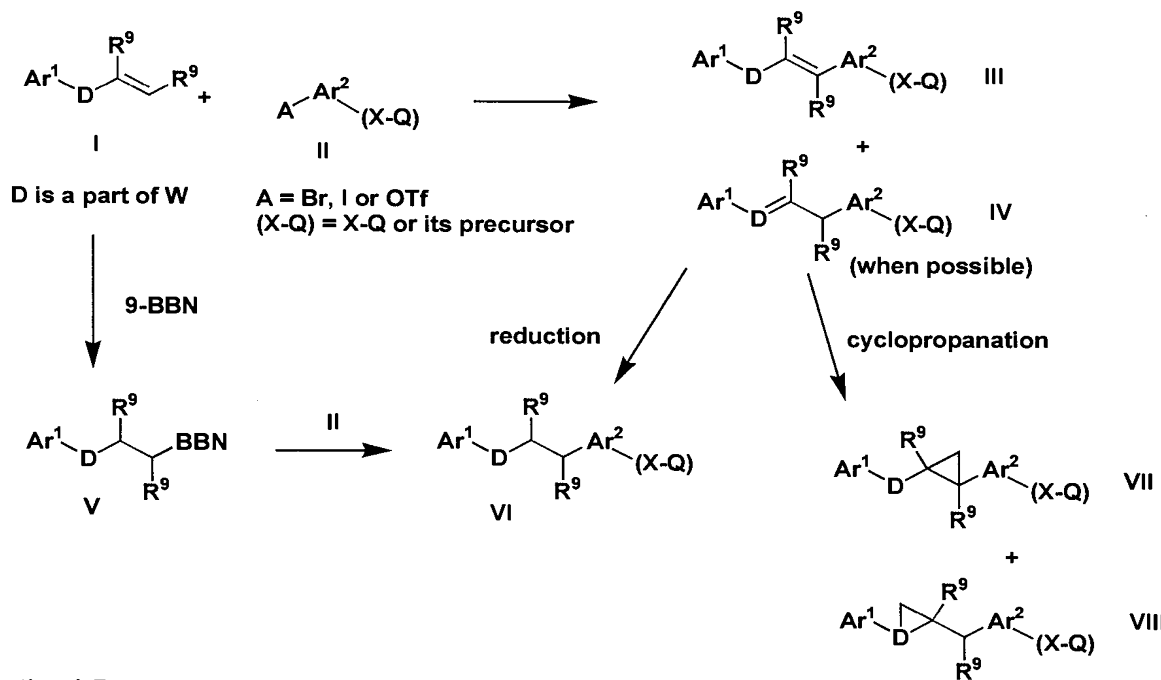
Examples of COX-2 selective compounds are such as those described in the following patents and published applications: WO96/25405, U.S.Pat. No. 5,633,272, WO97/38986, U. S. Pat. No. 5,466,823, WO98/03484, WO97/14691 and WO95/00501.

METHODS OF SYNTHESIS

Compounds of the present invention can be prepared according to the following methods. Methods A, I and J showed how to form the linker W between Ar^1 and Ar^2;methods B and E - H concentrate on linker X; method C explained how to obtain sulfonamides and method D illustrate how to substitute Ar^1. One particular method is usually used in conjunction with other methods to yield compounds of formula II. Reagents given below are for illustration of the chemistry only and should not be limiting this patent: other reagents might be as effective or better for each reaction described.

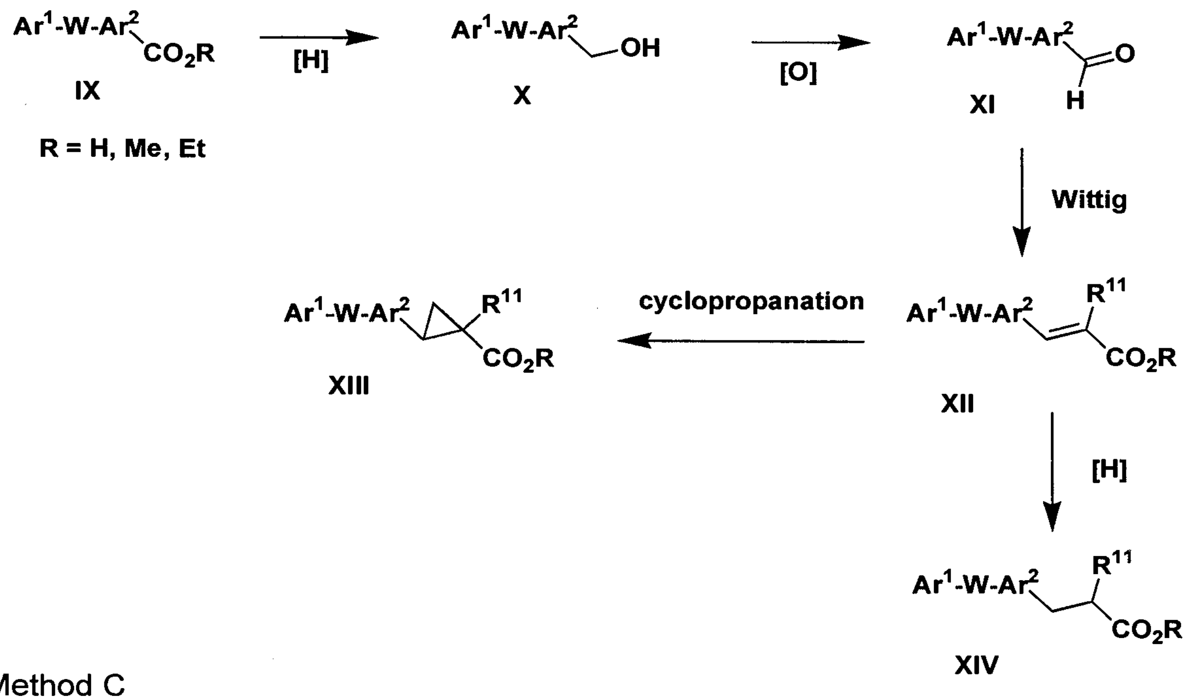
Method A

An aryl alkene I can be coupled with an aryl bromide, iodide or triflate II in the presence of a catalyst such as $Pd(OAc)_2$ to give the two isomers III and IV. Catalytic hydrogenation of the double bond, using Pd/C or $(Ph_3P)_3RhCl$, yield the compound VI. Alternatively, VI can be prepared from I via formation of the boronate V with 9-borabicyclo[3.3.1]nonane and coupling with II in the presence of a catalyst such as $PdCl_2(dppf)$. Cyclopropanation of the alkenes III and IV can be performed using conditions such as $CH_2N_2/PdOAc_2$ to give VII and VIII. The group X-Q in compounds III, IV, VI, VII and VIII can then be transformed to another X-Q group to afford other substructures of II.



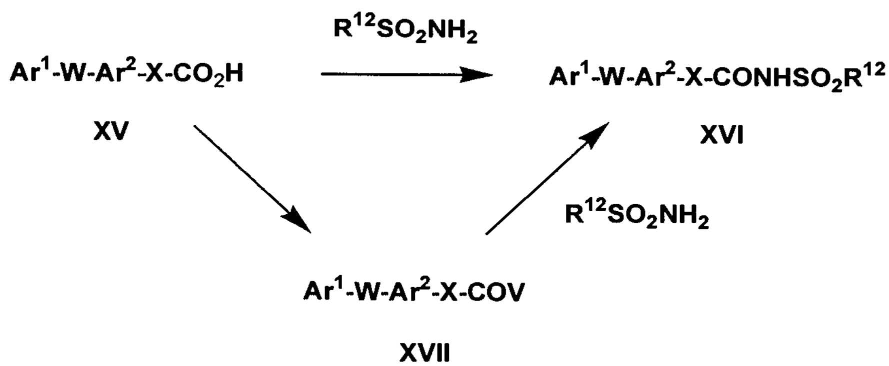
Method B

The acid or esters IX can be reduced to the alcohol X using reagents such as diisobutylaluminum hydride or sodium borohydride. Oxidation to the aldehyde XI can be performed using MnO_2 or pyridinium chlorochromate. Wittig reaction on XI afford the propenoate XII which can be cyclopropanated ($CH_2N_2/Pd(OAc)_2$) to XIII or reduced ($H_2/Pd/C$) to XIV. When R = H, compounds IX, XII, XIII and XIV are substructures of II.



Method C

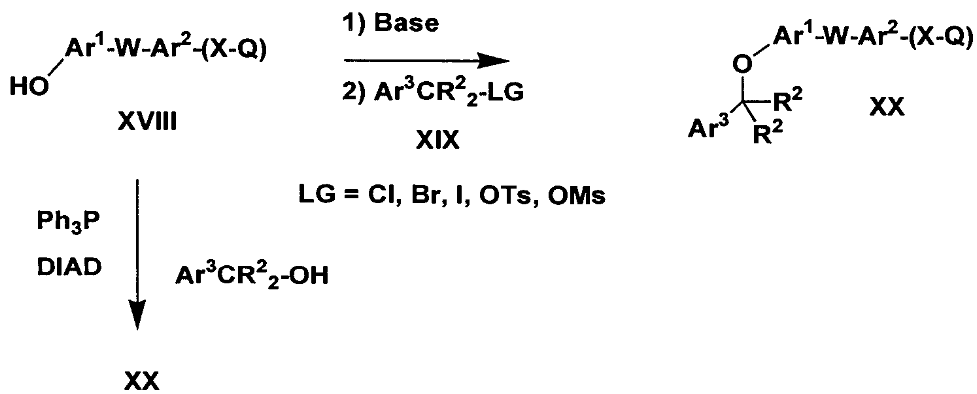
The acid XV, which is a substructure of II, can be transformed to the sulfonamide XVI, another substructure of II, by treatment with a sulfonamine in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Another method for the preparation of XVI involves the formation of an acid chloride or a mixed anhydride XVII and reaction with the sulfonamine in the presence of a base such as Et_3N.



V = Cl, Br, OCO_2alkyl

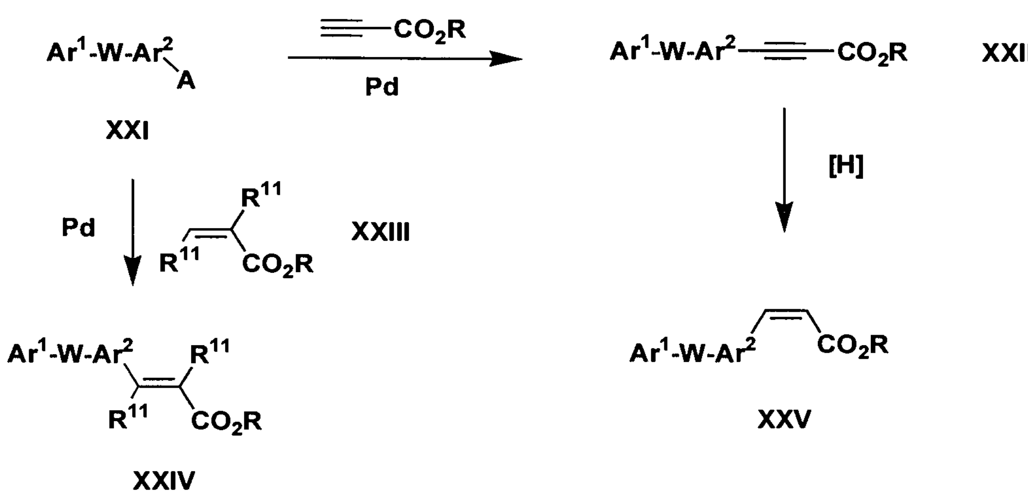
Method D

When compound II or its precursor is substituted by an hydroxyl group as in XVIII, it can be alkylated by a reagent containing a leaving group XIX in the presence of a base such as NaH or DBU to yield the ether XX. Alternatively, Mitsunobu reaction with the alcohol derivative of XIX also yield XX. The group X-Q in XX can then be transformed to another X-Q group to afford another example of II.



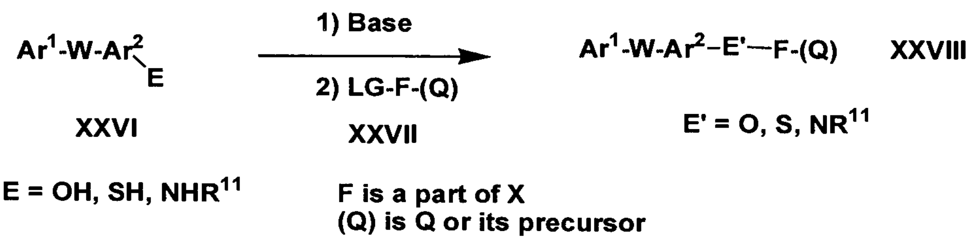
Method E

The aryl bromide, iodide or triflate XXI can be coupled with an alkyne or the alkene XXIII in the presence of a catalyst such as $Pd(OAc)_2$ (J. Org. Chem. 1979, 4078) to give the products XXII or XXIV respectively. Catalytic hydrogenation of the alkyne XXII over Lindlar's catalyst can afford the cis alkene XXV. When R = H, compounds XXII, XXIV and XXV are substructures of II and they can be treated as in method B to yield other examples of II.



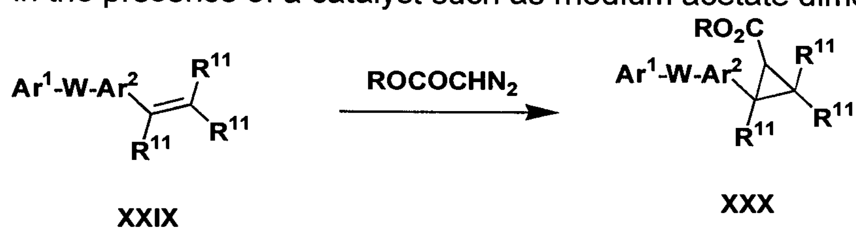
Method F

An aryl thiol, alcohol or amine XXVI can be treated with a base and then with reagent XXVII to yield the derivative XXVIII. The group E'-F-Q can be transformed to another E'-F-Q group using the other methods described here and yield examples of II possessing an heteroatom attached to Ar^2 in the linker X.



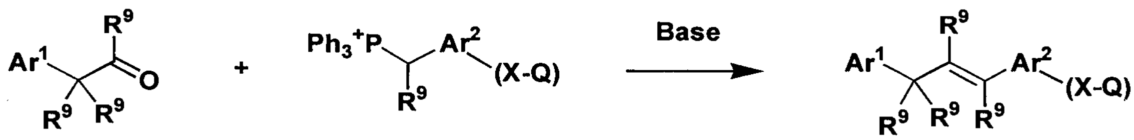
Method G

Compounds II possessing a cyclopropane unit as an X group XXX can be synthesized via a reaction between the alkene XXIX and a diazoacetate in the presence of a catalyst such as rhodium acetate dimer.

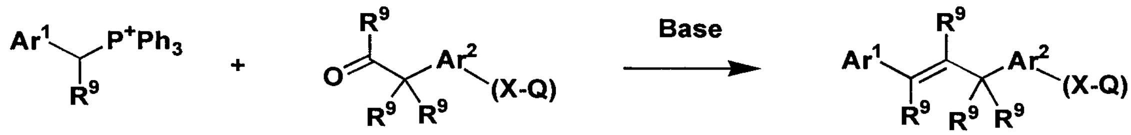


Method H

Compounds II possessing a double bond as part of the linker X can be synthesized via a Wittig reaction as exemplified in the next scheme. Phosphonium salts XXXII and XXXIV can be obtained from the corresponding Ar-CHR^9-LG by reaction with Ph_3P.



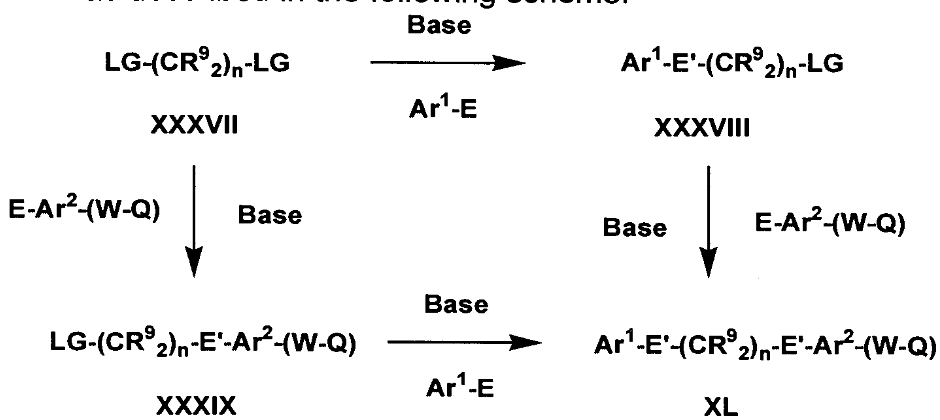
XXXI XXXII XXXIII



XXXIV XXXV XXXVI

<u>Method I</u>

Compounds II possessing two heteroatoms as part of the linker W as in XL can be synthesized from a reagent containing two leaving groups XXXVII and two aromatics compounds containing an alcohol, an amine or a thiol function E as described in the following scheme.



<u>Method J</u>

Compounds II possessing one heteroatom as part of the linker W as in XLV can be synthesized from a reagent containing one leaving group XLII or XLIII and an aromatic compound containing an alcohol, an amine or a thiol function E (XLI or XLIV) as described in the following two equations.

$$\underset{\textbf{XLI}}{Ar^1\text{-D-E}} + \underset{\textbf{XLII}}{LG\text{-D'-}Ar^2\text{-(X-Q)}} \xrightarrow{\text{Base}} \underset{\textbf{XLV}}{Ar^1\text{-D-E-D'-}Ar^2\text{-(X-Q)}}$$

$$\underset{\textbf{XLIII}}{Ar^1\text{-D-LG}} + \underset{\textbf{XLIV}}{E\text{-D'-}Ar^2\text{-(X-Q)}} \xrightarrow{\text{Base}} \underset{\textbf{XLV}}{Ar^1\text{-D-E-D'-}Ar^2\text{-(X-Q)}}$$

D and D' are part of W

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compound of Formula II can be tested using the following assays to determine their prostanoid antagonist or agonist activity *in vitro* and *in vivo* and their selectivity. The prostaglandin receptors investigated were DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

Stable expression of prostanoid receptors in the human embryonic kidney (HEK) 293(ebna) cell line

Prostanoid receptor cDNAs corresponding to full length coding sequences were subcloned into the appropriate sites of mammalian expression vectors and transfected into HEK 293(ebna) cells. HEK 293(ebna) cells expressing the individual cDNAs were grown under selection and individual colonies were isolated after 2-3 weeks of growth using the cloning ring method and subsequently expanded into clonal cell lines.

Prostanoid receptor binding assays

HEK 293(ebna) cells are maintained in culture, harvested and membranes are prepared by differential centrifugation, following lysis of the cells in the presence of protease inhibitors, for use in receptor binding assays. Prostanoid receptor binding assays are performed in 10 mM MES/KOH (pH 6.0) (EPs, FP and TP) or 10 mM HEPES/KOH (pH 7.4) (DP and IP), containing 1 mM EDTA, 10 mM divalent cation and the appropriate radioligand. The reaction is initiated by addition of membrane protein. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. Non-specific binding is determined in the presence of 1 μM of the corresponding non-radioactive prostanoid. Incubations are conducted for 60 min at room temperature or 30 °C and terminated by rapid filtration. Specific binding is calculated by subtracting non specific binding from total

binding. The residual specific binding at each ligand concentration is calculated and expressed as a function of ligand concentration in order to construct sigmoidal concentration-response curves for determination of ligand affinity.

Prostanoid receptor agonist and antagonist assays

Whole cell second messenger assays measuring stimulation (EP_2, EP_4, DP and IP in HEK 293(ebna) cells) or inhibition (EP_3 in human erythroleukemia (HEL) cells) of intracellular cAMP accumulation or mobilization of intracellular calcium (EP_1, FP and TP in HEK 293(ebna) cells stably transfected with apo-aequorin) are performed to determine whether receptor ligands are agonists or antagonists. For cAMP assays, cells are harvested and resuspended in HBSS containing 25 mM HEPES, pH 7.4. Incubations contain 100 μM RO-20174 (phosphodiesterase type IV inhibitor, available from Biomol) and, in the case of the EP_3 inhibition assay only, 15 μM forskolin to stimulate cAMP production. Samples are incubated at 37 C for 10 min, the reaction is terminated and cAMP levels are then measured. For calcium mobilization assays, cells are charged with the co-factors reduced glutathione and coelenterazine, harvested and resuspended in Ham's F12 medium. Calcium mobilization is measured by monitoring luminescence provoked by calcium binding to the intracellular photoprotein aequorin. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. For agonists, second messenger responses are expressed as a function of ligand concentration and both EC_{50} values and the maximum response as compared to a prostanoid standard are calculated. For antagonists, the ability of a ligand to inhibit an agonist response is determined by Schild analysis and both K_B and slope values are calculated.

Rat Paw Edema Assay

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, (1995)).

LPS-Induced Pyrexia in Conscious Rats

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, (1995)).

LPS-Induced Pyrexia in Conscious Squirrel Monkeys

The method is the same as described in Chan *et al* (Eur. J. Pharmacol. 327: 221- 225, (1997)).

Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

The method is the same as described in Boyce *et al* (Neuropharmacology 33: 1609-1611, (1994)).

Adjuvant-Induced Arthritis in Rats

Female Lewis rats (body weight ~146-170 g) were weighed, ear marked, and assigned to groups (a negative control group in which arthritis was not induced, a vehicle control group, a positive control group administered indomethacin at a total daily dose of 1 mg/kg and four groups administered with a test compound at total daily doses of 0.10-3.0 mg/kg) such that the body weights were equivalent within each group. Six groups of 10 rats each were injected into a hind paw with 0.5 mg of *Mycobacterium butyricum* in 0.1 mL of light mineral oil (adjuvant), and a negative control group of 10 rats was not injected with adjuvant. Body weights, contralateral paw volumes (determined by mercury displacement plethysmography) and lateral radiographs (obtained under Ketamine and Xylazine anesthesia) were determined before (day -1) and 21 days following adjuvant injection, and primary paw volumes were determined before (day -1) and on days 4 and 21 following adjuvant injection. The rats were anesthetized with an intramuscular injection of 0.03 - 0.1 mL of a combination of Ketamine (87 mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant. The radiographs were made of both hind paws on day 0 and day 21 using the Faxitron (45 kVp, 30 seconds) and Kodak X-OMAT TL film, and were developed in an automatic processor. Radiographs were evaluated for changes in the soft and hard tissues by an investigator who was blinded to experimental treatment. The following radiographic changes were graded numerically according to severity: increased soft issue volume (0-4), narrowing or widening of joint spaces (0-5) subchondral erosion (0-3), periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative joint changes (0-3). Specific criteria were used to establish the numerical grade of severity for each radiographic change. The maximum possible score per foot was 26. A test compound at total daily doses of 0.1, 0.3, 1, and 3

mg/kg/day, indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) were administered per os b.i.d. beginning post injection of adjuvant and continuing for 21 days. The compounds were prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

EXAMPLES

The invention is further illustrated in the following non-limiting examples in which, unless otherwise stated:

yields are given for illustration only and are not necessarily the maximum attainable;

all the end products of the formula II were analyzed by NMR, TLC and mass spectrometry;

intermediates were all analyzed by NMR and TLC;

most compounds were purified by flash chromatography on silica gel, recrystallization and/or swish (suspension in a solvent followed by filtration of the solid) with a solvent such as ether:hexane 1:1;

the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

temperatures are in degrees Celsius.

EXAMPLE 1

3-(2-(3-(2-(BENZYLOXY)-3-METHYLPHENYL)PROPYL)PHENYL)PROPANOIC ACID

A mixture of the products of examples 28 and 29 was dissolved in 2 ml MeOH:EtOAc 1:1 with *tris*(triphenylphosphine)rhodium(I) chloride (2mg) and the mixture hydrogenated under 60 psi of H_2. The reaction was followed by mass spectroscopy and, when completed, the solvent was evaporated and the product purified by flash chromatography with EtOAc:toluene containing 1% AcOH.

MS (APCI, neg.) 387.2 (M-1), 279.2.

EXAMPLES 2 AND 3

N2-((E)-3-(2-((E)-3-(2-(BENZYLOXY)-3-METHYLPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE

AND

N2-((E)-3-(2-((E)-3-(2-(BENZYLOXY)-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE

These acylsulfonamides were prepared from the cinnamic acids of examples 28 and 29 following the procedure of examples 44 and 45. MS (APCI, neg.) 528.2 (M-1).

EXAMPLES 6 AND 7

SODIUM (E)-3-(2-((E)-3-(2-(BENZYLOXY)PHENYL)-1-PROPENYL)PHENYL)-2-PROPENOATE

AND

SODIUM (E)-3-(2-((E)-3-(2-(BENZYLOXY)PHENYL)-2-PROPENYL)PHENYL)-2-PROPENOATE

Step 1 1-allyl-2-(benzyloxy)benzene

Sodium hydride 80% in oil (800 mg, 1.2 equiv.) was added to a solution of 2-allylphenol (2.998 g, 22 mmol) in DMF (40 ml) at 0 C and the mixture was stirred at 0°C for 15 min. and at r.t. for 1 h. Benzyl bromide (2.9 ml, 1.1 equiv.) was then added and the stirring was continued for 1 h. After hydrolysis with saturated NH_4Cl, the product was extracted in EtOAc, dried over Na_2SO_4, and concentrated to yield 5.01 g of an oil (yield 100%).

^{1}H NMR (Acetone-d_6) δ 3.40 (2H, d), 4.95 - 5.08 (2H, m), 5.13 (2H, s), 6.00 (1H, m), 6.90 (1H, dd), 7.03 (1H, d), 7.18 (2H, m), 7.32 (1H, m), 7.40 (2H, dd), 7.50 (2H, d).

Step 2 (E)-3-(2-((E)-3-(2-(benzyloxy)phenyl)-1-propenyl)phenyl)-2-propenoic acid and (E)-3-(2-((E)-3-(2-(benzyloxy)phenyl)-2-propenyl)phenyl)-2-propenoic acid

A mixture containing 2-bromocinnamic acid (250 mg, 1.10 mmol), the product of step 1 (271 mg, 1.1 equiv.), $Pd(OAc)_2$ (8 mg, 0.03 equiv.), LiCl (47 mg, 1 equiv.), LiOAc (280 mg, 2.5 equiv.) and Bu_4NCl (611 mg, 2 equiv.) in DMF (2 ml) was degassed and heated to 100 C o.n..0.5 N HCl was then added and the product was extracted in EtOAc, washed with

0.5 N HCl, dried over Na_2SO_4 and concentrated to dryness. Recrystallization from ether:hexane afforded the title product as a white solid. Yield: 251 mg, 62%.

^{1}H NMR (Acetone-d_6) δ 3.68 and 3.74 (2H, 2d), 5.10 and 5.20 (2H, 2s), 6.30 - 6.53 (2H, m), 6.70 - 6.93 (2H, m), 7.03 (1H, 2d), 7.18 (1H, m), 7.25 - 7.43 (7H, m), 7.50 (2H, m), 7.68 and 7.77 (1H, 2d), 8.03 (1H, 2d).

Step 3

The acids of step 2 were dissolved in EtOH and 1.0 equiv. of NaOH 1.0 N was added. The solvent was evaporated, the oil dissolved in water and the products were freeze-dried to afford a white solid.
MS (APCI, neg.) 369.0 (M-1)

The products of the following examples have been prepared in a manner similar to examples 6 and 7 and are mixtures of 2 compounds each.

Examples	Note	MS (APCI, neg.)[c]
8 & 9		429.1
10 & 11	d	411.2
12 & 13		399.1
14 & 15		399.1
16 & 17	a	371.1, 327.2 (M-CO_2H)
18 & 19	a	405.2, 361.0 (M-CO_2H)
21 & 22	d	443.1
23 & 24	d	307.1
25 & 26	d	263.1, 219.1 (M-CO_2H)
28 & 29	b	383.2
38 & 39	d	293.1, 234.0
40 & 41	d	323.1, 264.1
72 & 73		368.9, 233.2

a) Pd coupling (step 2) at 120°C o.n.,

b) the two products were separated by HPLC on a NovaPak C18 column,

c) M-1

d) the sodium salt was not prepared

EXAMPLE 20
2-(2-(3-(4-(BENZYLOXY)-3-METHOXYPHENYL)PROPYL)PHENYL)CYCLOPROPANE CARBOXYLIC ACID

Step 1 (E)-2-(2-(3-(4-(benzyloxy)-3-methoxyphenyl)propyl)phenyl)-2-propenoic acid

A solution of 9-borabicyclo[3.3.1]nonane 0.5 M in THF (3.8 ml, 1.5 equiv.) was added slowly to 4-allyl-1-benzyloxy-2-methoxybenzene (257 mg, 1.21 mmol, prepared as in examples 6 and 7, step 1) and the mixture was stirred at r.t. for 30 min. K_3PO_4 (384 mg), 2-bromocinnamic acid (222 mg, 978 mmol), (1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium(II) (31 mg) and DMF (4 ml) were added and the mixture was degassed and stirred at 50°C o.n.. A saturated solution of NH_4Cl was added, the solution was acidified with AcOH and the product was extracted in EtOAc, dried over Na_2SO_4 and partially purified by flash chromatography with EtOAc:toluene:AcOH 5:95:1.

Step 2 Methyl 2-(2-(3-(4-(benzyloxy)-3-methoxyphenyl)propyl)phenyl)cyclopropane-carboxylate

The acid of step 1 was treated with diazomethane in ether at reflux. The solvent was removed and the ester was purified by flash chromatography with EtOAc:toluene 2.5:97.5.

Step 3

The ester of step 2 was hydrolyzed with NaOH as in example 61, step 3. The final product was purified by HPLC with EtOAc:toluene:AcOH 2.5:97.5:1 on a μPorasil column to yield the title cyclopropaneacetic acid.

^{1}H NMR (acetone, d_6) δ 1.43 (2H, m), 1.76 (1H, m), 1.93 (2H, m), 2.55 (1H, m), 2.65 (2H, t), 2.82 (2H, m), 3.80 (3H, s), 5.07 (2H, s), 6.72 (1H, d), 6.87 (1H, s), 6.91 (1H, d), 7.03 (1H, d), 7.08 - 7.22 (3H, m), 7.28 - 7.41 (3H, m), 7.47 (2H, d). MS (APCI, neg.) 415.1 (M-1), 324.3.

EXAMPLE 27
(E)-3-(2-((E)-3-(2-HYDROXY-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

This product was obtained as a mixture with the other isomer (E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-1-propenyl)phenyl)-2-propenoic acid via a palladium coupling between 2-bromocinnamic acid and 2-alkyl-6-methylphenol as in examples 6 and 7, step 2. The title acid was separated from the other isomer by recrystallization from ether:hexane 1:1. Yield of pure product: 48%.

^{1}H NMR (Acetone-d_6) δ 2.20 (3H, s), 3.74 (2H, d), 6.34 ((1H, m), 6.44 (1H, d), 6.70 (1H, t), 6.80 (1H, d), 6.95 (1H, d), 7.22 (1H, d), 7.30 (1H, t), 7.35 (2H, m), 7.74 (1H, d), 8.10 (1H, d).

EXAMPLES 30 AND 31
(E)-3-(2-((E)-3-(2-((7-CHLORO-2-QUINOLINYL)METHOXY)-3-METHYLPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOIC ACID AND (E)-3-(2-((E)-3-(2-((7-CHLORO-2-QUINOLINYL)METHOXY)-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

Step 1 Methyl (E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-2-propenyl)phenyl)-1-propenyl)phenyl)-2-propenoate and methyl (E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-2-propenyl)phenyl)-2-propenyl)phenyl)-2-propenoate

These two products were prepared as a mixture via esterification of the two acids in example 27 using the procedure of example 61, step 1.

Step 2

Treatment of the two esters of step 1 with 7-chloro-2-(bromomethyl)quinoline (obtained by bromination of 7-chloroquinaldine with N-bromosuccinimide) and hydrolysis of the esters was performed as in example 61, steps 2 and 3.

MS (APCI, neg.) 470.0, 468.0 (M-1).

EXAMPLE 32

2-(3-(2-BENZYLOXY-3-METHYLPHENYL)PROPYL)BENZOIC ACID

3-Allyl-2-(benzyloxy)toluene (prepared as in examples 6 and 7, step 1) was treated with 9-BBN and then with ethyl 2-bromobenzoate as in example 20, step 1, to give the ester of the title compound. This ester was hydrolyzed as in example 61, step 3.

^{1}H NMR (acetone d_6) δ 1.95 (2H, m), 2.30 (3H, s), 2.75 (2H, m), 3.08 (2H, dd), 4.70 (2H, s), 6.92 - 7.12 (3H, m), 7.24 - 7.53 (8H, m), 7.93 (1H, d).

EXAMPLES 33 AND 34

SODIUM 2-(3-(2-BENZYLOXY-3-METHYLPHENYL)-1-PROPENYL)BENZOATE AND SODIUM 2-(3-(2-BENZYLOXY-3-METHYLPHENYL)-2-PROPENYL)BENZOATE

3-allyl-2-(benzyloxy)toluene (prepared as in examples 6 and 7, step 1) was coupled to ethyl 2-bromobenzoate as in examples 6 and 7, step 2. The resulting ester was hydrolyzed as in example 61, step 3.

^{1}H NMR (acetone d_6) δ 2.25 and 2.32 (3H, 2s), 3.64 and 3.97 (2H, 2d), 4.76 and 4.93 (2H, 2s), 6.33 and 6.50 (1H, 2td), 6.68 - 7.64 (12H, m), 7.90 and 7.98 (1H, 2d).

The sodium salts were prepared as in examples 6 and 7, step 3.

EXAMPLE 35

SODIUM (E)-3-(2-(3-(2-BENZYLOXY-3-METHYLPHENYL)PROPYL)PHENYL)-2-PROPENOATE

Step 1 2-(3-(2-benzyloxy-3-methylphenyl)propyl)benzaldehyde

3-al1yl-2-(benzyloxy)toluene was treated with 9-BBN and then with 2-bromobenzaldehyde as in example 20, step 1, to give the title aldehyde. Yield 58%.

Step 2 Ethyl (E)-3-(2-(3-(2-benzyloxy-3-methylphenyl)propyl)phenyl)-2-propenoate

To the aldehyde of step 1 (850 mg, 2.47 mmol) was added (methoxycarbonylmethylene)triphenylphosphorane (1.24 g, 1.5 equiv.) and the mixture was heated to 80 C in 25 ml of toluene for 10 h.

NH_4Cl was added and the mixture was extracted in EtOAc, dried over Na_2SO_4 and the product was purified by flash chromatography with EtOAc:toluene 2.5:97.5. Yield: 770 mg, 78%.

Step 3

Hydrolysis of the ester was performed as in example 61, step 3. MS (APCI, neg.) 385.1 (M-1).

The sodium salt was prepared as in examples 6 and 7, step 3.

The products of the following table were prepared in a manner similar to example 34.

Example #	MS (APCI, neg.)
36	401.2 (M-1), 310.0
37	401.2 (M-1), 310.0

EXAMPLE 42

SODIUM (E)-3-(2-((E)-3-(2-(BENZYLOXY)PHENYL)-3-HYDROXY-1-PROPENYL)PHENYL)-2-PROPENOATE

Step 1 1-(2-(benzyloxy)phenyl)-2-propen-1-ol

2-(benzyloxy)benzaldehyde (5g, 23.6 mmol) was reacted with vinylmagnesium bromide in THF (90 ml) at 0 C. The reaction was quenched with 2 N HCl and the product was extracted in i-PrOAc, dried over Na_2SO_4 and purified by flash chromatography with EtOAc:toluene 2.5:97.5.

Step 2

A mixture containing the allylic alcohol of step 1 (298 mg, 1.24 mmol), 2-bromocinnamic acid (299 mg, 1.06 equiv.), Bu_4NOAc (380 mg, 1 equiv.), Et_3N (1.2 ml), $PdCl_2(Ph_3P)_2$ (26 mg, 0.03 equiv.) and DMF (5 ml) was degassed and heated to 100 C for 2 h. After addition of NH_4Cl and acidification with AcOH, the product was extracted in EtOAc, dried over Na_2SO_4 and purified by flash chromatography with EtOAc:toluene:AcOH 10:90:5. Yield: 239 mg, 50%.

MS (APCI, neg.) 385.1 (M-1), 235.0

The sodium salt was prepared as in examples 6 and 7, step 3.

EXAMPLE 43

N2-((E)-3-(2-(3-(2-(BENZYLOXY)-3-METHYLPHENYL)PROPYL)PHENYL)-2-PROPANOYL)-2-THIOPHENESULFONAMIDE, SODIUM SALT

The mixture of the two acylsulfonamides of examples 2 and 3 were reduced by catalytic hydrogenation using 10% Pd/C in EtOAc at atmospheric pressure for 3 days. Filtration through celite and purification by flash chromatography yielded the title sulfonamide.

^{1}H NMR (Acetone-d_6) δ 1.85 (2H, m), 2.30 (3H, s), 2.60 (4H, m), 2.71 (2H, t), 2.85 (2H, t), 4.70 (2H, s), 6.92 - 7.13 (7H, m), 7.20 (1H, dd), 7.30 - 7.50 (5H, m), 7.80 (1H, d), 7.95 (1H, d). MS (APCI, neg.) 531.9 (M-1).

The sodium salt was prepared as in examples 6 and 7, step 3.

EXAMPLES 44 AND 45

N2-((E)-3-(2-((E)-3-(4-(BENZYLOXY)-3-METHOXYPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE AND N2-((E)-3-(2-((E)-3-(4-(BENZYLOXY)-3-METHOXYPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENE SULFONAMIDE, SODIUM SALTS

The product of examples 14 and 15 (254 mg, 634 μmol) was dissolved in 6 ml CH_2Cl_2. DMF (10 μl) and oxalyl chloride (76 ml, 1.4 equiv.) were then added at 0 C and the solution was stirred at r.t. for 1.5 h. The solvent was evaporated and the resulting acid chloride was redissolved in CH_2Cl_2 (6 ml). At 0 C, 2-thiophenesulfonamide (124 mg, 1.2 equiv.) and Et_3N (177 μl, 2 equiv.) were added and the mixture was stirred at 0 C for 1 h. 0.5 N HCl was then added and the product was extracted in i-PrOAc, dried over Na_2SO_4 and purified by flash chromatography on silica using EtOAc:toluene:AcOH 20:80:1. Yield: 201 mg, 58%.

MS (APCI, neg.) 544.2 (M-1).

The sodium salts were prepared as in examples 6 and 7, step 3.

EXAMPLE 46 AND 47
SODIUM (E)-3-(2-((2-(2-(BENZYLOXY)-3-METHYLPHENYL)CYCLOPROPYL)METHYL)PHENYL)-2-PROPENOATE AND SODIUM (E)-3-(2-(2-((2-(BENZYLOXY)-3-METHYLPHENYL)METHYL)CYCLOPROPYL) PHENYL)-2-PROPENOATE

Step 1 Ethyl 2-((2-(2-(benzyloxy)-3-methylphenyl)cyclopropyl)methyl)benzoate and ethyl 2-(2-((2-(benzyloxy)-3-methylphenyl)methyl)cyclopropyl)benzoate

The intermediate ester of example 33 was treated with portions of CH_2N_2 solution in ether and $Pd(OAc)_2$ alternatively and at 0 C until the reaction was complete. AcOH was added and the mixture was filtered through silica with ether and concentrated. This product was used as such in the next step.

Step 2 2-((2-(2-(benzyloxy)-3-methylphenyl)cyclopropyl)methyl)benzaldehyde and 2-(2-((2-(benzyloxy)-3-methylphenyl)methyl)cyclopropyl)benzaldehyde

To a solution of the ester of step 1 (3.68 mmol) in THF (20 ml) was added diisobutylaluminum hydride 1.0 M in toluene (16 ml, 4.4 equiv.) at -72 C and the mixture was stirred at -40 C for 10 min. The reaction was quenched with sodium potassium tartrate 1.0 M and was stirred at r.t. for 1.5 h. It was neutralized with AcOH and extracted in i-PrOAc. The product was dried over Na_2SO_4 and concentrated.

This benzylic alcohol was oxidized with activated MnO_2 (20 equiv.) in EtOAc at r.t. o.n. The mixture was then filtered through celite, concentrated and the aldehyde was purified by flash chromatography with toluene. Yield: 83% for steps 1 and 2.

Step 3

The aldehyde of step 2 was treated as in Example 34, steps 2 and 3, to afford the two title products. The sodium salts were prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 397.1 (M-1).

EXAMPLE 48

SODIUM (E)-3-(2-((E)-3-(2-BENZYLOXY-3-METHYLPHENYL)-3-HYDROXY-1-PROPENYL)PHENYL)-2-PROPENOATE

Step 1 Methyl (E)-3-(2-((E)-3-(2-benzyloxy-3-methylphenyl)-3-acetoxy-1-propenyl)phenyl)-2-propenoate and methyl (E)-3-(2-((E)-3-(2-benzyloxy-3-methylphenyl)-1-acetoxy-2-propenyl)phenyl)-2-propenoate.

The two products of examples 28 and 29 were esterified with NaH and MeI as in example 61, step 1. These esters (928 mg, 2.33 mmol) were heated to reflux in AcOH (15 ml) with SeO_2 (310 mg, 1.2 equiv.) for 15 min. After neutralization wit $NaHCO_3$, the products were extracted in EtOAc, dried over Na_2SO_4 and purified by flash chromatography with EtOAc:toluene 5:95.

Step 2 Methyl (E)-3-(2-((E)-3-(2-benzyloxy-3-methylphenyl)-3-hydroxy-1-propenyl)phenyl)-2-propenoate

The product of step 1 (2.3 mmol) was treated with 1.8-diazabicyclo[5.4.0]undec-7-ene (3 drops) in MeOH (10 ml) for 2 h. After evaporation, the title product was separated from the less polar cyclized isomer (methyl 2-(3-((E)-2-(2-(benzyloxy)-3-methylphenyl)-1-ethenyl)-1,3-dihydro-1-isobenzofuranyl)acetate) by flash chromatography with EtOAc:toluene 2.5:97.5 and 5:95.

Step 3

Hydrolysis was performed as in example 61, step 3. The sodium salt was prepared as in examples 6 and 7, step 3.
MS (APCI, neg.) 399.1 (M-1), 249.0.

EXAMPLES 50 AND 51

(E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-METHYLPHENYL)-3-HYDROXY-1-PROPENYL)PHENYL)-2-PROPENOIC ACID AND (E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-METHYLPHENYL)-1-HYDROXY-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

Step 1 (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzyloxy)-3-methylphenyl)-3-acetoxy-1-propenyl)phenyl)-2-propenoic acid and (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzyloxy)-3-methylphenyl)-1-acetoxy-2-propenyl)phenyl)-2-propenoic acid

The product of example 61 was treated with SeO_2 in AcOH as in example 48, step 1 to afford the two title acetates. Yield: 92%.

Step 2

The two acetates of step 1 (153 mg, 282 μmol) were heated in AcOH:H_2O 1:1 (14 ml) at 105 C for 45 min. After addition of NH_4Cl, the products were extracted in EtOAc, dried over Na_2SO_4 and purified by flash chromatography with EtOAc:toluene:AcOH 10:90:1. The two products were separated by HPLC on a NovaPak C18 cartridge using MeOH:(1:1 AcOH:AcONa 2 g/L) 7:3 and UV detection at 280 mm.

The more polar product was (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzyloxy)-3-methylphenyl)-1-hydroxy-2-propenyl)phenyl)-2-propenoic acid. Yield: 28 mg.

^1H NMR (acetone d_6) δ 2.10 (3H, s), 5.20 (2H, s), 5.73 (1H, d), 6.20 (1H, d), 6.47 (1H, dd), 6.97 (1H, t), 7.04 (1H, d), 7.10 (1H, d), 7.37 - 7.48 (6H, m), 7.63 (1H, d), 7.72 (1H, d), 8.35 (1H, d). MS (APCI, neg.) decomposition.

The less polar isomer was (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzyloxy)-3-methylphenyl)-3-hydroxy-1-propenyl)phenyl)-2-propenoic acid.

Yield: 17 mg.

MS (APCI, neg.) 467.0 (M-1), 291.0.

EXAMPLE 58 AND 59
(E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-(HYDROXYMETHYL)PHENYL)-1-PROPENYL)PHENYL)-2-PROPENOIC ACID AND (E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-(HYDROXYMETHYL)PHENYL)-2-PROPENYL)PHENYL)-2-PROPENOIC ACID

Step 1 3-allyl-2-(2,6-dichlorobenzyloxy)benzaldehyde

2-(allyloxy)benzaldehyde (2.00 g, 12.33 mmol) was heated in *o*-dichlorobenzene (20 ml) at reflux o.n. The mixture was poured on top of a flash chromatography column and eluted with toluene:hexane 1:1.

Yield: 1.346 g, 67%.

Step 2

The phenol of step 1 was treated with NaH and 2.6-dichlorobenzyl bromide as in examples 6 and 7, step 1, to give the benzyl ether. Then, the aldehyde was reduced with diisobutylaluminum hydride in THF at -10 C for 15 min. (see examples 46 and 47, step 2). Finally, a palladium coupling with 2-bromocinnamic acid was performed as in examples 6 and 7, step 2, to give the two title isomers.

Overall yield: 65%.

MS(APCI, neg.) 467.1 (M-1), 291.1.

EXAMPLE 61
SODIUM (E)-3-(2-((E)-3-(2-(2,6-DICHLOROBENZYLOXY)-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOATE

Step 1 Methyl (E)-3-(2-((E)-3-(2-hydroxy-3-methylphenyl)-2-propenyl)phenyl)-2-propenoate

The product of example 27 (2.001 g, 6.80 mmol) was dissolved in DMF (14 ml) and NaH 80% in oil (244 mg, 1.2 equiv.) was added at 0 C. The mixture was stirred for an hour at 0 C, then MeI (635 μl, 1.5 equiv.) was added and the stirring continued for 2 h. After hydrolysis with 0.5 N HCl, the product was extracted in EtOAc and purified by flash chromatography on silica with EtOAc:toluene 2.5:97.5 and 5:95. Yield: 1.70 g, 81%.

Step 2 Methyl (E)-3-(2-((E)-3-(2-(2,6-dichlorobenzyloxy)-3-methylphenyl)-2-propenyl)phenyl)-2-propenoate

The product of step 1 was treated with NaH and 2,6-dichlorobenzyl bromide as in examples 6 and 7, step 1, to afford the dichlorobenzyl ether.

Step 3

The ester (1.01 g, 2.18 mmol) was hydrolyzed with NaOH 10 N (930 μl) in THF:MeOH:H_2O 4:2:1 (28 ml) at r.t. o.n.. The reaction was quenched with sat. NH_4Cl, acidified with acetic acid and the product was extracted in EtOAc, concentrated and recrystallized in 20 ml ether:hexane 1:1. Yield: 746 mg, 75%.

The sodium salt was prepared as in examples 6 and 7, step 3.
MS (APCI, neg.) 452.0, 451.0 (M-1), 275.2.

The following compounds were prepared as in example 61.

Example #	MS(APCI, neg.)[a]
28	383.2
53	401.1, 275.2
55	419.1, 275.2
57	419.1, 275.2
63	451.1, 275.2
65	449.1, 275.2

a) M-1.

EXAMPLE 70
SODIUM (E)-3-(2-(3-PHENOXYBENZYLOXYMETHYL)PHENYL)-2-PROPENOATE

Step 1 Ethyl (E)-3-[2-(bromomethyl)phenyl]-2-propenoate

To a suspension of ethyl (E)-3-(2-methylphenyl)-2-propenoate (20.0 g; 105 mmol) and NBS (19.64 g; 110.3 mmol) in refluxing CCl_4 was added benzoyl peroxide (1.27 g) and the mixture was stirred for 12 h. The

solution was cooled to r.t., filtered and concentrated. Flash chromatography with EtOAc:hexane 5:95 yielded the title compound (14.18 g, 50%).

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t), 4.25 (2H, q), 4.60 (2H, s), 6.45 (1H, d), 7.30 (3H, m), 7.57 (1H, m) and 8.05 (1H, d).

Step 2 Ethyl (E)-3-(2-((3-phenoxy)benzyloxy)phenyl)-2-propenoate

To a solution of 3-phenoxybenzylalcohol (545 mg; 2.72 mmol) in DMF (5 ml) was added NaH (92 mg; 3.1 mmol; 80% dispersion in oil) and ethyl (E)-3-(2-(bromomethyl)phenyl)-2-propenoate (810 mg; 3.0 mmol). After 6 h at r.t., 20 mg extra NaH was added. The final mixture was stirred at r.t. for 10 h then quenched using 0.3 ml of AcOH. The mixture was diluted with Et_2O (25 ml), washed with water (3 x 20 ml) and brine, dried over $MgSO_4$ and concentrated. Flash chromatography with EtOAc:toluene 5:95 afforded the desired material.

Yield: 822 mg, 78%.

Step 3

The ester of step 2 was hydrolyzed as in example 61, step 3, to yield the title acid. The sodium salt was prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 359.0 (M-1).

EXAMPLE 71

SODIUM (E)-3-(2-(2-PHENOXYBENZYLOXYMETHYL)PHENYL) -2-PROPENOATE

This product was prepared as in example 70 from 2-phenoxybenzyl alcohol.

MS (APCI, neg.) 359.0 (M-1).

EXAMPLE 74

SODIUM (E)-3-(2-(3-(2-BENZYLOXYPHENOXY)PROPOXY)PHENYL)-2-PROPENOATE

Step 1 Methyl (E)-3-(2-(3-bromopropoxy)phenyl)-2-propenoate

To a solution of methyl 2-hydroxycinnamate (1.31 g; 7.33 mmol) in 50 ml acetone was added 1,3-dibromopropane (1.50 ml; 14.8 mmol) and K_2CO_3 (4.36 g; 13.4 mmol). The mixture was heated to reflux for 12h, cooled to r.t, diluted with hexane (50 ml), filtered and finally concentrated to afford the title product (1.96 g; 50% pure), which was used as such in the next step.

Step 2

2-Benzyloxyphenol (obtained from catechol, NaH, and benzyl bromide as in examples 6 and 7, step 1) was treated with NaH and the product of step 1 as in examples 6 and 7, step 1 to afford the ester of the title product. This ester was hydrolyzed as in example 61, step 3 to yield the acid. The sodium salt was prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 403.1 (M-1), 233.1, 207.1.

EXAMPLE 75

SODIUM (E)-3-(2-((E)-3-(2-(1-PHENYLETHOXY)-3-METHYLPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOATE

1-Phenylethanol was obtained by reduction of acetophenone with $NaBH_4$ in THF:MeOH. It was then reacted with the ester of example 61, step 1, via a Mitsunobu reaction (DIAD, Ph_3P, THF:CH_2Cl_2, Synth. Commun. 1994, 24, 1049), to yield the ester of the title compound. This ester was hydrolyzed as in example 61, step 3, to give the title acid.

The sodium salt was prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 397.1 (M-1), 293.0, 275.3, 233.2.

EXAMPLES 77 AND 78

SODIUM (E)-3-(2-((E)-3-(3-PHENOXYPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOATE AND SODIUM (E)-3-(2-((E)-3-(3-PHENOXYPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOATE

Step 1 1-bromo-3-phenoxybenzene

To a solution of phenol (5.08g; 54mmol) in 30 ml dry DMF at $0^{o}C$ was added portionwise NaH (1.98 g; 66 mmol; 80% dispersion in oil). The mixture was stirred 30 min at r.t. then 1,3-dibromobenzene (33 ml; 273 mmol) and Cu_2O (3.95 g; 28 mmol) were added. The final mixture was heated to reflux for 4h, cooled to r.t., diluted with Et_2O (200 ml), washed with water (3 x 200 ml), NaOH (1.0 M; 2 x 100 ml) and brine, dried over $MgSO_4$ and concentrated. Flash chromatography with hexane afforded the desired material.

Yield: 7.62 g, 57%.

Step 2 1-allyl-3-phenoxybenzene

A suspension of 1-bromo-3-phenoxybenzene (2.01 g; 8.08 mmol), $PdCl_2(PPh_3)_2$ (296 mg ; 0.42 mmol), allyl tributyltin (3.13 g ; 9.46 mmol), triphenylphosphine (455 mg; 1.73 mmol) and LiCl (1.39 g; 33 mmol) in 10 ml DMF was stirred at $100^{o}C$ for 3h. After cooling to r.t the mixture was diluted with Et_2O (75 ml), washed with water (3 x 50 ml) and brine, dried over $MgSO_4$ and concentrated. Flash chromatography with hexane afforded the desired material.

Yield: 1.39g, 81%.

Step 3

Using the procedure of examples 6 and 7, steps 2 and 3, the product of step 2 was transformed to the title compounds.

MS (APCI, neg.) 355.1 (M-1), 311.2.

EXAMPLES 79 AND 80

SODIUM (E)-3-(2-((E)-3-(3-PHENYLBENZO[*B*]FURAN-7-YL)-1-PROPENYL)PHENYL)-2-PROPENOATE AND SODIUM (E)-3-(2-((E)-3-(3-PHENYLBENZO[*B*]FURAN-7-YL)-2-PROPENYL) PHENYL)-2-PROPENOATE

Step 1 2-(2-bromophenoxy)-1-phenyl-1-ethanone

To a solution of 2-bromophenol (8.71 g; 50.3 mmol) and bromoacetophenone (10.1 g; 50.5 mmol) in 50 ml acetone was added K_2CO_3 (7.02 g; 50.8 mmol). The mixture was heated to reflux for 10 h, cooled to r.t., filtered, diluted with EtOAc (100 ml), washed with HCl (1.0 M, 2 x 100 ml) and brine, dried over $MgSO_4$ and concentrated. The residual solid was recrystallized from EtOAc:hexane to afford the desired material.

Yield: 11.6 g, 79%.

Step 2 3-phenylbenzo[*b*]furan-7-yl-bromide

A mixture of 2-(2-bromophenoxy)-1-phenyl-1-ethanone (6.31 g) and polyphosphoric acid (285 g) was stirred at 95°C for 6 h. The resulting solution was cooled to 50°C, poured in water (2 L), extracted with Et_2O (2 x 1 L). The combined organic extracts were washed with water (4 x 500 ml) and brine, dried over $MgSO_4$ and concentrated. The residual solid was filtered on a plug of silica gel using Et_2O. Recrystallization in hot hexane yielded the title compound (4.63g; 78%).

Step 3

Using the procedure of examples 77 and 78, steps 2 and 3, the bromide of step 2 was transformed to the title acid. The sodium salts were prepared as in examples 6 and 7, step 3.

MS (APCI, neg.) 379.4 (M-1), 335.1.

EXAMPLES 81 AND 82

N2-((E)-3-(2-((E)-3-PHENYL-1-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE AND N2-((E)-3-(2-((E)-3-PHENYL-2-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE

These acylsulfonamides were prepared from the cinnamic acids of examples 25 and 26 following the procedure of Synlett 1995, 1141.

MS (APCI, neg.) 408.2 (M-1).

EXAMPLES 83 AND 84

N2-((E)-3-(2-((E)-3-(4-METHOXYPHENYL)-1-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE AND N2-((E)-3-(2-((E)-3-(4-METHOXYPHENYL)-2-PROPENYL)PHENYL)-2-PROPENOYL)-2-THIOPHENESULFONAMIDE

These acylsulfonamides were prepared from the cinnamic acids of examples 38 and 39 following the procedure of Synlett 1995, 1141.

MS (APCI, neg.) 438.1 (M-1), 233.2.

WHAT IS CLAIMED IS:

1. A compound represented by formula II:

$$Ar^1\text{-}W\text{-}Ar^2\text{-}X\text{-}Q$$

II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar^1 is an aryl or heteroaryl group, optionally substituted with R^1 or R^3;

R^1 is Y_m-R^2, Y_m-Ar^3, halogen, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, $CON(R^5)_2$, $S(O)_nR^7$ or OH;

Y represents a linker between R^2 or Ar^3 and Ar^1 containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker optionally containing CO, $S(O)_n$, -C=C- or an acetylenic group, and said linker being optionally substituted by R^2;

m is 0 or 1;

n is 0, 1 or 2;

R^2 represents H, F, CHF_2, CF_3, lower alkyl or hydroxyC_{1-6} alkyl, or two R^2 groups may be joined together and represent a carbocyclic ring of up to six members, said ring containing not more than one heteroatom selected from O, N and S;

Ar^3 represents an aryl or heteroaryl group, optionally substituted with R^3 ;

R^3 is R^4, halogen, haloC_{1-6}alkyl, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, $CON(R^5)_2$, OR^4, SR^4 or $S(O)_nR^7$;

R^4 is H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3 ;

R^5 is R^4, Ph or Bn, or two R^5 groups in combination with the atom to which they are attached represent a ring of up to 6 members containing carbon atoms and up to 2 heteroatoms selected from O, N and S;

R^6 is H, F, CF_3 or lower alkyl, or two R^6 groups may be taken together and represent a ring of up to 6 members containing carbon atoms and 0-2 heteroatoms selected from O, N and S;

R^7 is lower alkyl, lower alkenyl, lower alkynyl, CHF_2, CF_3, $N(R^5)_2$, $Ph(R^8)_2$ or $CH_2Ph(R^8)_2$;

R^8 is R^4, OR^4, SR^4 or halogen

W represents a 3-6 membered linking group containing 0 to 2 heteroatoms selected from O, N and S, said linking group optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and optionally being substituted with R^9;

R^9 is R^2, lower alkenyl, lower alkynyl, OR^4 or SR^4;

Ar^2 represents an aryl or heteroaryl group, optionally substituted with R^3;

R^{10} represents R^4, halogen, $N(R^5)_2$, CN, NO_2, $C(R^6)_3$, OR^4, SR^4 or $S(O)_nR^7$;

X represents a linker which is attached to Ar^2 ortho to the attachment of W, said linker containing 0-4 carbon atoms and not more than one heteroatom selected from O, N and S, said linker further optionally containing CO, $S(O)_n$, C=C or an acetylenic group, and said linker being optionally substituted with R^{11};

R^{11} is R^9;

Q represents a member selected from the group consisting of: CO_2H, tetrazole, SO_3H, hydroxamic acid, $CONHSO_2R^{12}$ and SO_2NHCOR^{12};

R^{12} represents a member selected from the group consisting of: CF_3, lower alkyl, lower alkenyl, lower alkynyl and ZAr^4 , wherein Z is an optional linker containing 0-4 carbon atoms, optionally substituted with R^{13};

R^{13} is R^9;

Ar^4 is an aryl or heteroaryl group optionally substituted with R^{14}, and

R^{14} is R^{10} or NHCOMe.

2. A compound in accordance with claim 1 wherein R^1 is OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 or $NR^2CH_2Ar^3$.

3. A compound in accordance with claim 1 wherein Ar^3 is an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R^3.

4. A compound in accordance with claim 1 wherein Ar^2 is an aryl or heteroaryl group selected from the group consisting of: benzene,

pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with 1-5 groups selected from R^4, OR^4, SR^4 and halogen.

5. A compound in accordance with claim 1 wherein W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, $CH(OH)CH{=}CH$, $CH{=}CHCH(OH)$, $CH_2C{+}C$, $C{+}CCH_2$, 1,2-c-Pr-CH_2 and -1,2-c-Pr-CH_2-.

6. A compound in accordance with claim wherein X is selected from the group consisting of: $(CH_2)_2$, $CH{=}CH$, $C{+}C$ and 1,2-c-Pr.

7. A compound in accordance with claim 1 wherein Q is CO_2H or tetrazole.

8. A compound in accordance with claim 1 wherein Z represents a 0-2 carbon atom linker that is unsubstituted.

9. A compound in accordance with claim 1 wherein Ar^4 represents an aryl or heteroaryl group selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, said group being optionally substituted with R^3.

10. A compound in accordance with claim 1 wherein:

Ar^1 is an aryl or heteroaryl group substituted by R^1 and R^3;

R^1 is OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 or $NR^2CH_2Ar^3$;

Ar^3 is selected from the group consisting of benzene, pyridine, thiophene, furan, oxazole and thiazole, said group being optionally substituted with R^3;

Ar^2 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, and thiazole, said group being optionally substituted with 1-4 members selected from the group consisting of: R^4, OR^4, SR^4 and halogen;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, $CH(OH)CH{=}CH$, $CH{=}CHCH(OH)$, $CH_2C{+}C$, $C{+}CCH_2$ 1,2-c-Pr-CH_2- and -CH_2-1,2-c-Pr-;

X is selected from the group consisting of: $(CH_2)_2$, CH=CH, C+C and 1,2-c-Pr;

and Q is CO_2H or tetrazole.

11. A compound in accordance with claim 1 wherein:

Ar^1 is an aryl or heteroaryl group optionally substituted with R^1 and R^3;

R^1 is OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 or $NR_2CH_2Ar^3$;

Ar^3 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being optionally substituted with R^3;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, CH_2CH=CH, CH=$CHCH_2$, CH(OH)CH=CH, CH=CHCH(OH), CH_2C+C or C+CCH_2;

Ar^2 represents a member selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole or thiazole, said group being optionally substituted with R^8;

X is is selected from the group consisting of: $(CH_2)_2$, CH=CH, C+C and 1,2-c-Pr;

Q is $CONHSO_2ZAr^4$;

Z is a 0-2 carbon linker and is unsubstituted;

Ar^4 is selected from the group consisting of: benzene, pyridine, thiophene, furan, oxazole, thiazole, 1,3,4-thiadiazole and naphthalene, and is optionally substituted by R^3.

12. A compound in accordance with claim 1 wherein:

Ar^1 is benzene or thiophene substituted in position 2 and/or position 4 relative to the attachment of W with a member selected from the group consisting of: OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 and $NR^2CH_2Ar^3$, and is optionally substituted in position 3 with a member selected from the group consisting of: OMe, $OCHF_2$ and lower alkyl;

Ar^3 is benzene or thiophene, optionally substituted with R^8;

W is selected from the group consisting of: CH_2OCH_2, $(CH_2)_3$, CH_2CH=CH, CH=$CHCH_2$, CH(OH)CH=CH and CH=CHCH(OH),

Ar^2 is benzene or thiophene, optionally substituted with 1-4 members selected from R4, OR4, SR4 and halogen;

X represents a member selected from the group consisting of: $(CH_2)_2$, CH=CH and 1,2-c-Pr, and

Q is CO_2H.

13. A compound in accordance with claim 1 wherein:

Ar^1 is a benzene or a thiophene unsubstituted or substituted in position 2 and/or position 4 relative to the point of attachment to W by a member selected from the group consisting of: OH, OCH_2Ar^3, SCH_2Ar^3, OAr^3, SAr^3 and $NR^2CH_2Ar^3$; and is optionally substituted at position 3 with one member selected from the group consisting of: OMe, $OCHF_2$ and lower alkyl;

Ar^3 is benzene or thiophene, optionally substituted with R^8;

W is selected from the group consisting of: CH_2OCH_2 , $(CH_2)_3$, $CH_2CH{=}CH$, $CH{=}CHCH_2$, CH(OH)CH=CH and CH=CHCH(OH);

Ar^2 is benzene or thiophene, optionally substituted with R4, OR4, SR4 or halo;

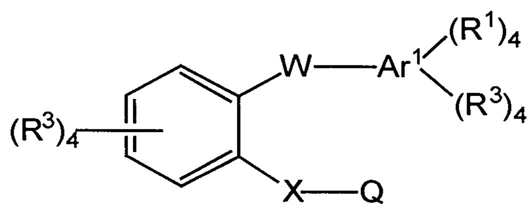
X is selected from the group consisting of: $(CH_2)_2$, CH=CH and 1,2-c-Pr,

Q is $CONHSO_2ZAr^4$,

Z is a bond or CH_2, and

Ar^4 is selected from the group consisting of: benzene, thiophene, 1,3,4-thiadiazole and naphthalene and is substituted with R^8.

14. A compound represented by formula II':



II'

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar^1 represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;

R^1 represents H, OH, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;

R^3 represents R^4, halogen, OR^4 or SR^4;

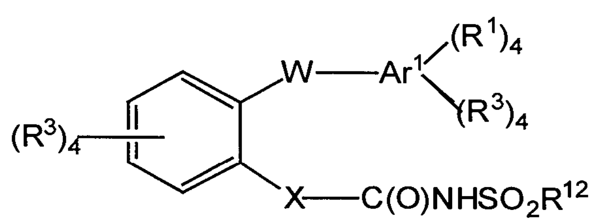
R^4 represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3;

X represents a member selected from the group consisting of: $-(CH_2)_{1-2}-$, 1,2-c-Pr, -CH=CH-, $-CH_2O-$, $-C{+}CCH_2-$, -C+C-, and $-CH_2-C{+}C-$;

W represents a member selected from the group consisting of: $-(CH_2)_{3-6}-$, $-CH_2CH{=}CH-$, $-CH{=}CHCH_2-$, -CH(OH)CH=CH-, -CH=CHCH(OH)-, $-CH_2$-1,2-c-Pr-, -1,2-c-Pr-CH_2-, , $-CH_2-O-CH_2-$, $-O-(CH_2)_{1-3}-O-$, $-CH_2$-NHC(O)-, $-CF_2CH{=}CH-$, $-CH{=}CHCF_2-$, $-CH_2CH_2-S-$, $-S-CH_2CH_2-$, $-CH_2CH_2-SO_2-$, $-SO_2-CH_2CH_2-$, $-O-(CH_2)_{1-3}-$, $-(CH_2)_{1-3}-O-$ and $-CH{=}CHCH_2CH_2-$, and

all other variables are as defined in claim 1.

15. A compound represented by formula II":



II"

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Ar^1 represents phenyl, naphthyl, benzofuranyl or methylenedioxyphenyl;

R^1 represents H, OH, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, aryl, aryloxy, arylalkoxy, haloaryl, haloheteroaryl, haloarylalkoxy, alkylaryl, haloalkylarylalkoxy, haloarylalkoxy and haloheteroarylalkoxy;

R^3 represents R^4, halogen, OR^4 or SR^4;

R^4 represents H, lower alkyl, lower alkenyl, lower alkynyl, CHF_2 or CF_3;

X represents a member selected from the group consisting of: $-(CH_2)_{1-2}-$, -1,2-c-Pr-, -CH=CH-, $-CH_2O-$, $-C{+}CCH_2-$, $-C{+}C-$, and $-CH_2-C{+}C-$;

W represents a member selected from the group consisting of: $-(CH_2)_{3-6}-$, $-CH_2CH=CH-$, $-CH=CHCH_2-$, -CH(OH)CH=CH-, -CH=CHCH(OH)-, $-CH_2$-1,2-c-Pr-, -1,2-c-Pr-CH_2-, $-CH_2-O-CH_2-$, $-O-(CH_2)_{1-3}-O-$, $-CH_2-NHC(O)-$, $-CF_2CH=CH-$, $-CH=CHCF_2-$, $-CH_2CH_2-S-$, $-S-CH_2CH_2-$, $-CH_2CH_2-SO_2-$, $-SO_2-CH_2CH_2-$, $-O-(CH_2)_{1-3}-$, $-(CH_2)_{1-3}-O-$ and $-CH=CHCH_2CH_2-$, and

R^{12} is selected from the group consisting of: C_{1-6}alkyl, thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl, -CH=CH-phenyl, said thienyl, phenyl, naphthyl, biphenyl, quinolinyl, thiadiazolyl, tetrazolyl and -CH=CH-phenyl groups being optionally substituted with R^3.

16. A compound in accordance with claim 1 falling within the following table:

Table I					
(Ar^1-W-Ar^2-X-Q)					
Ex	Ar^1	W	Ar^2	X	Q
1	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	$(CH_2)_2$	CO_2H
2	2-(BnO)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	$CONHSO_2$-2-thienyl
3	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-2-thienyl
4	2-((2-Cl-4-FPh)CH_2O)-3-CF_3Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
5	2-((2-Cl-4-FPh)CH_2O)-3-CF_3Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
6	2-(BnO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CO_2^-\ X^+$

7	2-(BnO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2^- X^+
8	4-(BnO)-3,5-$(MeO)_2$Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2^- X^+
9	4-(BnO)-3,5-$(MeO)_2$Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2^- X^+
10	2-(BnO)-5-AcPh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
11	2-(BnO)-5-AcPh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
12	2-(BnO)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2^- X^+
13	2-(BnO)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2^- X^+
14	4-(BnO)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2^- X^+
15	4-(BnO)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2^- X^+
16	2-(BnO O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH_2	CO_2^- X^+
17	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH_2	CO_2^- X^+
18	2-(BnO)-3-MePh	$CH_2CH=CH$	5-Cl-1,2-Phe	CH_2	CO_2^- X^+
19	2-(BnO)-3-MePh	$CH=CHCH_2$	5-Cl-1,2-Phe	CH_2	CO_2^- X^+
20	4-(BnO)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	1,2-c-Pr	CO_2H
21	2-(BnO)-3-MePh	$CH=CHCH_2$	4,5-$(MeO)_2$-1,2-Phe	CH=CH	CO_2H
22	2-(BnO)-3-MePh	$CH_2CH=CH$	4,5-$(MeO)_2$-1,2-Phe	CH=CH	CO_2H
23	3,4-(methylene dioxy)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
24	3,4-(methylene dioxy)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
25	Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
26	Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
27	2-(HO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
28	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2^- X^+
29	2-(BnO)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2^- X^+
30	2-((7-Cl-2-quinolinyl)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
31	2-((7-Cl-2-quinolinyl)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
32	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	bond	CO_2H
33	2-(BnO)-3-MePh	$CH=CHCH_2$	1,2-Phe	bond	CO_2^- X^+
34	2-(BnO)-3-MePh	$CH_2CH=CH$	1,2-Phe	bond	CO_2^- X^+
35	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	CH=CH	CO_2^- X^+
36	2-(BnO)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	CO_2^- X^+

37	4-(BnO)-3-(MeO)Ph	$(CH_2)_3$	1,2-Phe	CH=CH	$CO_2^- X^+$
38	4-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
39	4-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
40	3,4-$(MeO)_2$Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
41	3,4-$(MeO)_2$Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
42	2-(BnO)Ph	CH(OH)CH=CH	1,2-Phe	CH=CH	$CO_2^- X^+$
43	2-(BnO)-3-MePh	$(CH_2)_3$	1,2-Phe	$(CH_2)_2$	$CON^- X^+ SO_2$-2-thienyl
44	4-(BnO)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CON^- X^+ SO_2$-2-thienyl
45	4-(BnO)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	$CON^- X^+ SO_2$-2-thienyl
46	2-(BnO)-3-MePh	CH_2-1,2-c-Pr	1,2-Phe	CH=CH	$CO_2^- X^+$
47	2-(BnO)-3-MePh	1,2-c-Pr-CH_2	1,2-Phe	CH=CH	$CO_2^- X^+$
48	2-(BnO)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	$CO_2^- X^+$
49	2-(BnO)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
50	2-((2,6-Cl_2Ph)CH_2O)-3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
51	2-((2,6-Cl_2Ph) CH_2O)-3-MePh	CH(OH)CH=CH	1,2-Phe	CH=CH	CO_2H
52	2-((4-FPh)CH_2O)-3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
53	2-((4-FPh)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	$CO_2^- X^+$
54	2-((3,4-F_2Ph)CH_2O) -3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
55	2-((3,4-F_2Ph)CH_2O) -3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	$CO_2^- X^+$
56	2-((3,5-F_2Ph)CH_2O) -3-MePh	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
57	2-((3,5-F_2Ph)CH_2O) -3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	$CO_2^- X^+$
58	2-((2,6-Cl_2Ph)CH_2O) -3-($HOCH_2$)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	CO_2H
59	2-((2,6-Cl_2Ph)CH_2O) -3-($HOCH_2$)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H

60	2-((2,6-Cl_2Ph)CH_2O) -3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
61	2-((2,6-Cl_2Ph)CH_2O) -3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
62	2-((4-CF_3Ph)CH_2O) -3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
63	2-((4-CF_3Ph)CH_2O) -3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
64	2-((4-(CHF_2O)Ph) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
65	2-((4-(CHF_2O)Ph) CH_2O)-3-MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
66	2-((4-CF_3Ph)CH_2O) -3-(HOCH_2)Ph	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
67	2-((4-CF_3Ph)CH_2O) -3-(HOCH_2)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
68	2-((4-CF_3Ph)CH_2O) -3-MePh	CH=CHCH(OH)	1,2-Phe	CH=CH	CO_2H
69	2-(PhCH_2O)-3-(HOCH_2)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2H
70	3-(PhO)Ph	CH_2OCH_2	1,2-Phe	CH=CH	CO_2^- X^+
71	2-(PhO)Ph	CH_2OCH_2	1,2-Phe	CH=CH	CO_2^- X^+
72	3-(BnO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2^- X^+
73	3-(BnO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
74	2-(BnO)Ph	O$(CH_2)_3$O	1,2-Phe	CH=CH	CO_2^- X^+
75	2-(PhCHMeO)-3 -MePh	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
76	2-(PhCHMeO)-3 -MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
77	3-(PhO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
78	3-(PhO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2^- X^+
79	3-Phbenzo furan-7-yl	CH=CHCH_2	1,2-Phe	CH=CH	CO_2^- X^+
80	3-Phbenzo furan-7-yl	CH_2CH=CH	1,2-Phe	CH=CH	CO_2^- X^+
81	Ph	CH=CHCH_2	1,2-Phe	CH=CH	CONHSO_2 -2-thienyl
82	Ph	CH_2CH=CH	1,2-Phe	CH=CH	CONHSO_2 -2-thienyl
83	4-(MeO)Ph	CH=CHCH_2	1,2-Phe	CH=CH	CONHSO_2-2-thienyl
84	4-(MeO)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CONHSO_2-2-thienyl

85	2-(BnO)-1-naphthyl	CH_2NHCO	1,2-Phe	CH=CH	CO_2H
86	2-((2-Cl-4-FPh) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
87	2-((2-Cl-4-FPh) CH_2O)-3-MePh	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2H
88	2-((2,4-F_2Ph)CH_2O) -3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
89	2-((2,4-F_2Ph) CH_2O)-3-MePh	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2H
90	2-((2,4,6-F_3Ph) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
91	2-((2,4,6-F_3Ph) CH_2O)-3-MePh	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2H
92	2-((2,6-Cl_2-4-FPh) CH_2O)-3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
93	2-((2,6-Cl_2-4-FPh) CH_2O)-3-MePh	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2H
94	2-((2,4-F_2Ph)CH_2O) -3-(CHF_2O)Ph	CH_2CH=CH	1,2-Phe	CH=CH	CO_2H
95	2-((2,4-F_2Ph)CH_2O) -3-(CHF_2O)Ph	CH=$CHCH_2$	1,2-Phe	CH=CH	CO_2H
96	2-((4-FPh)CH_2O) -3-MePh	CF_2CH=CH	1,2-Phe	CH=CH	CO_2H
97	2-((4-FPh)CH_2O) -3-MePh	CH=$CHCF_2$	1,2-Phe	CH=CH	CO_2H
98	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_3$	1,2-Phe	CH=CH	$CONHSO_2$-(4-i-PrPh)
99	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_3$	1,2-Phe	CH=CH	$CONHSO_2$-(4-t-BuPh)
100	2-((4-FPh)CH_2O) -3-MePh	CH_2CH=CH	1,2-Phe	CH=CH	$CONHSO_2$-(4-(MeO)Ph)
101	2-((4-FPh)CH_2O) -3-MePh	CH=$CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2,3-Cl_2Ph)
102	2-((4-FPh)CH_2O) -3-MePh	CH=$CHCH_2$	4-Cl-1,2-Phe	CH=CH	$CONHSO_2$-(5-Br-2-(MeO)Ph)
103	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_2S$	3-F-1,2-Phe	CH=CH	$CONHSO_2$-(2,3,4-Cl_3Ph)
104	2-((4-FPh)CH_2O)-3-MePh	$(CH_2)_2S$	6-CF_3-1,2-Phe	CH=CH	$CONHSO_2$-(5-F-2-MePh)
105	2-((4-FPh)CH_2O)-3-MePh	$(CH_2)_2S$	4,5-F_2-1,2-Ph	CH=CH	$CONHSO_2$-(2,5-Me_2Ph)
106	2-((4-FPh)CH_2O)-3-MePh	$(CH_2)_2SO_2$	1,2-Phe	CH=CH	$CONHSO_2$-(4-CF_3Ph)
107	2-((4-FPh)CH_2O)-3-MePh	$(CH_2)_2SO_2$	1,2-Phe	CH=CH	$CONHSO_2$-2-naphthyl

108	2-((4-FPh)CH2O)-3-MePh	CH=CHCH2	3-F-1,2-Phe	CH=CH	CONHSO2-(3-Cl-4-FPh)
109	2-((4-FPh)CH2O)-3-MePh	SO2(CH2)2	1,2-Phe	CH=CH	CONHSO2-(4-n-PrPh)
110	2-((4-FPh)CH2O)-3-(MeO)Ph	SO2(CH2)2	1,2-Phe	CH=CH	CONHSO2-(2-ClPh)
111	2-((4-FPh)CH2O)-3-(MeO)Ph	SO2(CH2)2	1,2-Phe	CH=CH	CONHSO2-(4-FPh)
112	2-((4-FPh)CH2O)-3-(MeO)Ph	S(CH2)2	1,2-Phe	CH=CH	CONHSO2-(2-PhPh)
113	2-((4-FPh)CH2O)-3-(MeO)Ph	S(CH2)2	1,2-Phe	CH=CH	CONHSO2-(2-CF3Ph)
114	2-((4-FPh)CH2O)-3-(MeO)Ph	S(CH2)2	4-t-Bu-1,2-Phe	CH=CH	CONHSO2-(4-Cl-2,5-Me2Ph)
115	2-((4-FPh)CH2O)-3-(MeO)Ph	O(CH2)2	1,2-Phe	CH=CH	CONHSO2-(2,5-Cl2Ph)
116	2-((4-FPh)CH2O)-3-(MeO)Ph	O(CH2)2	1,2-Phe	CH=CH	CONHSO2-(4-Br-2-(CF3O)Ph)
117	2-((4-FPh)CH2O)-3-(MeO)Ph	O(CH2)2	1,2-Phe	CH=CH	CONHSO2-CH2Ph
118	2-((4-FPh)CH2O)-3-(MeO)Ph	(CH2)2O	1,2-Phe	CH=CH	CONHSO2-1-naphthyl
119	2-((4-FPh)CH2O)-3-(MeO)Ph	(CH2)2O	4,5-F2-1,2-Phe	CH=CH	CONHSO2-(2-FPh)
120	2-((4-FPh)CH2O)-3-(MeO)Ph	(CH2)2O	1,2-Phe	CH=CH	CONHSO2-(2,4-Cl2Ph)
121	2-((4-FPh)CH2O)-3-(MeO)Ph	(CH2)3	1,2-Phe	CH=CH	CONHSO2-CH=CHPh
122	2-((4-FPh)CH2O)-3-(MeO)Ph	(CH2)3	1,2-Phe	CH=CH	CONHSO2-(3,5-(CF3)2Ph)
123	2-((4-FPh)CH2O)Ph	(CH2)3	1,2-Phe	CH=CH	CONHSO2-(2,5-Cl2-3-thienyl)
124	2-((4-FPh)CH2O)Ph	(CH2)4	3-F-1,2-Phe	CH=CH	CONHSO2-(3-BrPh)
125	2-((4-FPh)CH2O)Ph	(CH2)4	3-MeO-1,2-Phe	CH=CH	CONHSO2-(2-BrPh)
126	2-((4-FPh)CH2O)Ph	(CH2)4	1,2-Phe	CH=CH	CONHSO2-(2-NO2Ph)
127	2-((4-FPh)CH2O)Ph	(CH2)5	1,2-Phe	(CH2)2	CONHSO2-(3-ClPh)
128	2-((4-FPh)CH2O)Ph	(CH2)5	1,2-Phe	(CH2)2	CONHSO2-(4-(CF3O)Ph)
129	2-HOPh	CH=CH(CH2)2	1,2-Phe	(CH2)2	CONHSO2-8-quinolinyl
130	2-((4-FPh)CH2O)Ph	CH=CH(CH2)2	5-(CF3O)-1,2-Phe	(CH2)2	CONHSO2-(3,4-Cl2Ph)

131	4-((2,6-Cl_2-4-FPh)CH_2O)-3-MePh	$CH=CH(CH_2)_2$	3-F-1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(4-EtPh)
132	2-((4-FPh)CH_2O)Ph	$CH_2CH=CH$	1,2-Phe	$(CH_2)_2$	$CONHSO_2$-(4-Cl-2-NO_2Ph)
133	2-((4-FPh)CH_2O)Ph	$CH=CHCH_2$	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(2-Cl-3-Br-5-thienyl)
134	2-((4-FPh)CH_2O)Ph	$CH_2CH=CH$	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(3,4-$(MeO)_2$Ph)
135	2-HOPh	$CH=CHCH_2$	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(2,5-Cl_2-3-Br-4-thienyl)
136	4-((4-FPh)CH_2O)-3-(MeO)Ph	$CH_2CH=CH$	4,5-F_2-1,2-Phe	CH=CH	$CONHSO_2$-(4-Br-2,5-F_2Ph)
137	4-((4-FPh)CH_2O)-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-(5-(AcNH)-1,3,4-thiadiazol-2-yl)
138	4-((4-FPh)CH_2O)-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CONHSO_2$-(2,3,4,5,6-F_5Ph)
139	4-((2-Cl-4-FPh)CH_2O)-3-MePh	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2-CNPh)
140	2-((4-FPh)CH_2O)Ph	$CH_2CH=CH$	4-F-1,2-Phe	CH=CH	$CONHSO_2$-(2-Cl-6-MePh)
141	2-HOPh	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-(2,4,6-Me_3Ph)
142	Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CONHSO_2$-(2,3-Br_2-2-thienyl)
143	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	CH_2O	$CONHSO_2$-(4-NO_2Ph)
144	2-((4-FPh) CH_2O)Ph	$CH_2CH=CH$	1,2-Phe	CH_2O	$CONHSO_2$-(3,5-Cl_2Ph)
145	2,4-((4-FPh) $CH_2O)_2$Ph	$CH=CHCH_2$	1,2-Phe	prop-1-yne-1,3-diyl	$CONHSO_2$-(5-Cl-2-thienyl)
146	4-((2,4-F_2Ph)CH_2O) -3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	CH_2O	$CONHSO_2$-(4-CF_3Ph)
147	2-HO-3-MePh	$CH=CHCH_2$	1,2-Phe	CH_2O	$CONHSO_2$-(2,4-F_2Ph)
148	2-((4-FPh)CH_2O)Ph	$CH_2CH=CH$	4-F-1,2-Phe	1,2-ethyne diyl	$CONHSO_2$-(4-ClPh)
149	2-((4-FPh)CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	1,2-ethyne diyl	$CONHSO_2$-(3-CF_3Ph)
150	4-HOPh	$CH_2CH=CH$	1,2-Phe	1,2-ethyne diyl	$CONHSO_2$-Ph
151	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	prop-2-yne-1,3-diyl	$CONHSO_2$-(5-Br-2-thienyl)

152	2,4-((4-FPh) $CH_2O)_2Ph$	$CH_2CH=CH$	1,2-Phe	1,2-ethynediyl	$CONHSO_2$-Me
153	2,4-((4-FPh) $CH_2O)_2Ph$	$CH=CHCH_2$	1,2-Phe	1,2-c-Pr	$CONHSO_2$-(2,5-$(MeO)_2Ph$)
154	6-((4-FPh)CH_2O)-2-naphthyl	$CH_2CH=CH$	4-F-1,2-Phe	1,2-c-Pr	$CONHSO_2$-(3-MePh)
155	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	1,2-c-Pr	$CONHSO_2$-(4-MePh)
156	4-HO-3-(MeO)Ph	$CH_2CH=CH$	1,2-Phe	1,2-c-Pr	$CONHSO_2$-n-Bu
157	4-((4-FPh)CH_2O) -1-naphthyl	$CH=CHCH_2$	1,2-Phe	1,2-c-Bu	$CONHSO_2$-(2-Cl-4-FPh)
158	Ph	$CH_2CH=CH$	1,2-Phe	CH=CH	$CONHSO_2$-(2-MePh)
159	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	$CONHSO_2$-c-Pr
160	2,4-((4-FPh) $CH_2O)_2Ph$	$CH=CHCH_2$	1,2-Phe	CH=CH	CO_2H
161	4-((2,4-F_2Ph) CH_2O)-3-(MeO)Ph	$(CH_2)_3$	4-F-1,2-Phe	CH=CH	1H-tetrazol-5-yl
162	2-((4-FPh) CH_2O)Ph	$CH=CHCH_2$	3-MeO-1,2-Phe	CH=CH	1H-tetrazol-5-yl
163	2,4-((4-FPh) $CH_2O)_2Ph$	$CH=CHCH_2$	1,2-Phe	CH=CH	1H-tetrazol-5-yl
164	4-HO-3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	1,2-c-Pr	1H-tetrazol-5-yl
165	Ph	$CH=CHCH_2$	1,2-Phe	$(CH_2)_2$	1H-tetrazol-5-yl
166	2-((4-FPh)CH_2O) -3-(MeO)Ph	$CH=CHCH_2$	1,2-Phe	CH=CH	SO_3H
167	2-((4-FPh)CH_2O) -3-MePh	$(CH_2)_3$	4-F-1,2-Phe	$(CH_2)_2$	SO_3H

wherein X^+ represents a cation.

17. A compound in accordance with claim 16 wherein X^+ represents a cation selected from the group consisting of: ammonium, calcium, magnesium, potassium and sodium.

18. A pharmaceutical composition comprised of a compound in accordance with any one of claims 1 to 17 in combination with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition in accordance with claim 18 further comprising a COX-2 selective inhibiting compound.

20. A method of treating or preventing a prostaglandin mediated disease in a mammalian patient in need thereof, comprising admininstering to said patient a compound in accordance with claim 1 in an amount which is effective for treating or preventing said prostaglandin mediated disease.

21. A method of treating or preventing a prostaglandin mediated disease in accordance with claim 20 further comprising administering to said patient an effective amount of a COX-2 selective inhibiting compound.

22. A method of treating or preventing a prostaglandin mediated disease in accordance with claim 20 wherein the prostaglandin mediated disease is selected from the group consisting of:
Pain, fever, inflammation, rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains, strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout, ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures, immune and autoimmune diseases, cellular neoplastic transformations, metastatic tumor growth, prostaglandin-mediated proliferation disorders such as diabetic retinopathy and tumor angiogenesis, dysmenorrhea, premature labor, asthma, eosinophil related disorders, Alzheimer's disease, glaucoma, bone loss (osteoporosis), promotion of bone formation (treatment of fractures) and other bone diseases such as Paget's disease.

23. A method of treating or preventing an E type prostaglandin mediated disease in a mammalian patient, comprising administering to said patient an amount of an E type prostaglandin ligand in an amount which is effective to treat or prevent said E type prostaglandin mediated disease.

24. A method in accordance with claim 23 further comprising administering a COX-2 selective inhibitor.

25. An antagonist of pain and inflammatory effects of E-type prostaglandins pharmaceutical composition, comprising an acceptable antagonizing amount of a compound of formula II, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any of claims 1 to 17, in association with a pharmaceutically acceptable carrier.

26. A compound of formula II, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any of claims 1 to 17, for use in the prevention or treatment of prostaglandin mediated diseases in a mammalian patient.

27. Use of a compound of formula II, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any of claims 1 to 17, in the manufacture of a medicament for the treatment or prevention of prostaglandin mediated diseases in a mammalian patient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00926

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C59/66 C07C309/10 C07C311/51 C07C323/60 C07C323/62
C07D215/14 C07D215/36 C07D257/04 C07D285/12 C07D307/79
C07D317/60 C07D333/34 A61K31/192 A61K31/381

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 780 061 A (A. ALLAIS, ET AL.) 18 December 1973 (1973-12-18) column 26, line 40 - line 57	1,3-5,7
X	CH 407 101 A (J.R. GEIGY) 31 August 1966 (1966-08-31) page 2, line 35	1,3-5,7
X	US 3 641 133 A (E.E. GALANTAY, ET AL.) 8 February 1972 (1972-02-08) example 15	1,3-5,7
X	US 4 922 022 A (J. DIXON, ET AL.) 1 May 1990 (1990-05-01) column 9, line 34 - line 35	1,3-5,7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 1999	11/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	J.M. SPRINGER, ET AL.: "The reaction of 1-tetralones with potassium hydroxide-sodium hydroxide" JOURNAL OF ORGANIC CHEMISTRY, vol. 35, no. 5, May 1970 (1970-05), pages 1260-1264, XP002126076 American Chemical Society, Washington, DC, US ISSN: 0022-3263 compounds 17-20	1
X	R.F. REKKER, ET AL.: "Ultraviolet absorption spectra of some aromatic tricyclic ketones" RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, vol. 90, 1971, pages 343-351, XP000857564 Elsevier Science Publishers, Amsterdam, NL ISSN: 0165-0513 page 350, line 16 - line 21	1,3-5,7
A	WO 96 06822 A (ZENECA) 7 March 1996 (1996-03-07) cited in the application page 1 -page 3	1,18,20, 23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00926

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: not applicable

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds having values of the variables Ar1, W, Ar2, X and Q illustrated in examples 1-3, 6-48, 50, 51, 58, 59, 61, 70-75, 77-84 (ie. those compounds of claim 16 with at least one physical property reported in the description).

Even after this limitation, the search revealed such a large number of particularly relevant documents, in particular with regard to novelty, that the drafting of a comprehensive International Search Report is not feasible. The cited documents are considered as to form a representative sample of the revealed documents, duly taking into account their relevance with respect to the subject-matter as illustrated by the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/CA 99/00926

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3780061 A	18-12-1973	FR 2138257 A	05-01-1973
		BE 783720 A	20-11-1972
		CA 996105 A	31-08-1976
		DE 2224655 A	07-12-1972
		GB 1374491 A	20-11-1974
		NL 7206898 A	23-11-1972
CH 407101 A		NONE	
US 3641133 A	08-02-1972	NONE	
US 4922022 A	01-05-1990	AT 80151 T	15-09-1992
		AU 614749 B	12-09-1991
		AU 1706788 A	21-12-1988
		CA 1294289 A	14-01-1992
		DE 3874206 A	08-10-1992
		DK 728388 A	12-01-1989
		EP 0292202 A	23-11-1988
		EP 0314725 A	10-05-1989
		FI 890207 A	16-01-1989
		WO 8809326 A	01-12-1988
		IL 86411 A	29-03-1992
		JP 1503303 T	09-11-1989
		NO 890187 A	16-01-1989
		NZ 224676 A	28-05-1991
		PT 87503 A,B	31-05-1989
		US 4939147 A	03-07-1990
WO 9606822 A	07-03-1996	AT 185791 T	15-11-1999
		AU 3351995 A	22-03-1996
		DE 69512925 D	25-11-1999
		EP 0778821 A	18-06-1997
		JP 10504836 T	12-05-1998
		US 5965741 A	12-10-1999